INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/05153

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61K31/70, A61K9/00, A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61K31/70, A61K9/00, A61K9/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 6-192107, A (SANWA KAGAKU KENKYUSHO CO., LTD.), 12 July, 1994 (12.07.94), especially, Claims (Family: none)	1-8
Y	JP, 10-226650, A (ONO PHARMACEUTICAL CO., LTD.), 25 August, 1998 (25.08.98), especially, Claims (Family: none)	1-8
Y	JP, 3-255037, A (SANTEN PHARMACEUTICAL CO., LTD.), 13 November, 1991 (13.11.91), especially, Claims (Family: none)	1-8
Y	JP, 58-501174, A (Tillotts Pharma. AG.), 21 July, 1983 (21.07.83), especially, Claims & EP, 97651, A1 & GB, 2123695, A & US, 5541171, A & US, 5541170, A	1-3

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December, 1999 (10.12.99)	21 December, 1999 (21.12.99)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/05153

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 9-87169, A (TANABE SEIYAKU CO., LTD.), 31 March, 1997 (31.03.97), especially, Claims & EP, 754452, A2	1,2,4
Y	F. Takahashi, "Recent Progress in Drug Delivery System", Journal of Medicine, Vol. 34, S-1, 01 January, 1998 (01.01.98), pages 237-242	1,2,4
Y	Wilson, Clive G. et.al, 'Evaluation of a gastro-resistant pulsed release delivery system (Pulsincap) in humans', Drug Delivery, Vol.4, No.3, (1997), p.201-206	1,2,5
Y	S. Masuda, K. Takada, "The Latest Drug Delivery System to the Large Intestine ", PHARM TECH JAPAN, Vol. 11, No.11,(1995), pages 37-46	1,2,6
Y	WO, 94/10983, A1 (HISAMITSU PHARMACEUTICAL CO., INC.), 26 May, 1994 (26.05.94), especially, Claims & US, 5654004, A & EP, 667148, A1	1,2,6
Y	JP, 8-253413, A (Kanji Takada), 01 October, 1996 (01.10.96), especially, Claims & US, 5637319, A	1,2,7,8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/05153

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claim 9 relates to a method for treatment of the human body by therapy or operation.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ９９／０５１５３

第Ⅰ欄　請求の範囲の一部の調査ができないときの意見（第１ページの２の続き）

法第８条第３項（ＰＣＴ１７条(2)(a)）の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1．[X] 請求の範囲 ＿＿＿9＿＿＿は、この国際調査機関が調査をすることを要しない対象に係るものである。
つまり、
請求の範囲９は、人の手術又は治療による処置方法に関するものである。

2．[ ] 請求の範囲 ＿＿＿＿＿＿＿＿は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、

3．[ ] 請求の範囲 ＿＿＿＿＿＿＿＿は、従属請求の範囲であってＰＣＴ規則6.4(a)の第２文及び第３文の規定に従って記載されていない。

第Ⅱ欄　発明の単一性が欠如しているときの意見（第１ページの３の続き）

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

1．[ ] 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。

2．[ ] 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。

3．[ ] 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったので、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。

4．[ ] 出願人が必要な追加調査手数料を期間内に納付しなかったので、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意

[ ] 追加調査手数料の納付と共に出願人から異議申立てがあった。

[ ] 追加調査手数料の納付と共に出願人から異議申立てがなかった。

国際調査報告

国際出願番号 PCT／JP99／05153

A. 発明の属する分野の分類（国際特許分類（IPC））

Int.Cl[6] A61K31/70, A61K9/00, A61K9/48

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int.Cl[6] A61K31/70, A61K9/00, A61K9/48

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CA（STN）

C. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
Y	JP, 6－192107, A（株式会社三和化学研究所）, 12. 7月. 1994（12. 07. 94）, 特に特許請求の範囲（ファミリーなし）	1－8
Y	JP, 10－226650, A（小野薬品工業株式会社）, 25. 8月. 1998（25. 08. 98）, 特に特許請求の範囲（ファミリーなし）	1－8
Y	JP, 3－255037, A（参天製薬株式会社）, 13. 11月. 1991（13. 11. 91）, 特に特許請求の範囲（ファミリーなし）	1－8

☒ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
10. 12. 99	21.12.99

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）	4C	9454
日本国特許庁（ISA／JP） 郵便番号100－8915 東京都千代田区霞が関三丁目4番3号	上條 のぶよ 電話番号 03－3581－1101 内線 3450		

様式PCT／ISA／210（第2ページ）（1998年7月）

国際調査報告

国際出願番号 PCT／JP99／05153

C（続き）. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
Y	JP, 58－501174, A（ジェー・ビー・ティロット・リミテッド）, 21. 7月. 1983（21. 07. 83）, 特に特許請求の範囲 & EP, 97651, A1 & GB, 2123695, A & US, 5541171, A & US, 5541170, A	1－3
Y	JP, 9－87169, A（田辺製薬株式会社）, 31. 3月. 1997（31. 03. 97）, 特に特許請求の範囲 & EP, 754452, A2	1, 2, 4
Y	高橋保志, 「最近の Drug Delivery System の進歩」, 医薬ジャーナル, Vol.34, S-1, 1. 1月. 1998（01. 01. 98）, p. 237－242	1, 2, 4
Y	Wilson, Clive G. et.al, 'Evaluation of a gastro-resistant pulsed release delivery system (Pulsincap) in humans', Drug Delivery, Vol.4, No.3, (1997), p. 201－206	1, 2, 5
Y	増田茂樹, 高田寛治, 「最新の薬物大腸デリバリー技術」, PHARM TECH JAPAN, Vol.11, No.11, (1995), p. 37－46	1, 2, 6
Y	WO, 94／10983, A1（久光製薬株式会社）, 26. 5月. 1994（26. 05. 94）, 特に特許請求の範囲 & US, 5654004, A & EP, 667148, A1	1, 2, 6
Y	JP, 8－253413, A（高田寛治）, 1. 10月. 1996（01. 10. 96）, 特に特許請求の範囲 & US, 5637319, A	1, 2, 7, 8

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 9-87169, A (TANABE SEIYAKU CO., LTD.), 31 March, 1997 (31.03.97), especially, Claims & EP, 754452, A2	1,2,4
Y	F. Takahashi, "Recent Progress in Drug Delivery System", Journal of Medicine, Vol. 34, S-1, 01 January, 1998 (01.01.98), pages 237-242	1,2,4
Y	Wilson, Clive G. et al., 'Evaluation of a gastro-resistant pulsed release delivery system (Pulsincap) in humans', Drug Delivery, Vol.4, No.3, (1997), p.201-206	1,2,5
Y	S. Masuda, K. Takada, "The Latest Drug Delivery System to the Large Intestine ", PHARM TECH JAPAN, Vol. 11, No.11, (1995), pages 37-46	1,2,6
Y	WO, 94/10983, A1 (HISAMITSU PHARMACEUTICAL CO., INC.), 26 May, 1994 (26.05.94), especially, Claims & US, 5654004, A & EP, 667148, A1	1,2,6
Y	JP, 8-253413, A (Kanji Takada), 01 October, 1996 (01.10.96), especially, Claims & US, 5637319, A	1,2,7,8

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 03-255037
(43)Date of publication of application : 13.11.1991

(51)Int.Cl. A61K 47/14
A61K 9/48
A61K 9/52
A61K 31/70
A61K 31/70
A61K 31/70

(21)Application number : 02-052350
(22)Date of filing : 02.03.1990

(71)Applicant : SANTEN PHARMACEUT CO LTD
(72)Inventor : MORITA TAKAKAZU
MITA SHIRO
KAWASHIMA YOICHI

(54) GLYCYRRHIZIN PHARMACEUTICAL PREPARATION

(57)Abstract:
PURPOSE: To obtain a glycyrrhizin preparation capable of quickly increasing the concentration of glycyrrhizin in blood by blending glycyrrhizin or salt thereof with a fatty acid glyceride and coating the blend with an enteric coating film.
CONSTITUTION: Glycyrrhizin or salts thereof is blended with a fatty acid glyceride (e.g. mono, di or triglyceride of middle chain fatty acid such as stearic acid or caprylic acid) at a ratio of (1:1)–(1:10.0) and the blend is coated with an enteric coating film (e.g. hydroxypropylmethylcellulose phthalate) to provide a glycyrrhizin preparation having a form of tablet, granule, inhalant, capsule, etc. When the preparation is administered, glycyrrhizin is rapidly absorbed in the duodenum or small intestine, because the enteric coating film is dissolved in the duodenum and moved into blood to effectively exhibit the effect. Glycyrrhizin is effective in the therapy of liver disease, allergic disease, etc.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of r jection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 10-226650
(43)Date of publication of application : 25.08.1998

(51)Int.Cl. A61K 31/70
A61K 47/12

(21)Application number : 09-049824
(22)Date of filing : 18.02.1997

(71)Applicant : ONO PHARMACEUT CO LTD
(72)Inventor : YAMAMOTO MASANOBU
KIN JUNJI
TERAJIMA HIROSHI

(54) GLYCYRRHIZIN ORAL PREPARATION

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a glycyrrhizin oral preparation capable of importing glycyrrhizin in the oral preparation to blood without degradation in digestive tract by allowing the release of the glycyrrhizin or a salt thereof and an absorption promoter from the oral preparation to be carried out in a dissolved state at the bottom of the digestive tract.
SOLUTION: This glycyrrhizin oral preparation is the one obtained by coating glycyrrhizins as a principal ingredient, and an absorption promoter with an enteric coating material. The absorption promoter is a middle chain fatty acid, e.g. capric acid or an alkali metal salt thereof, especially capric acid or sodium caprate, and polyethylene glycol, propylene glycol, distilled water, etc., are used as a solubilizing agent. The formulating mol ratio of the glycyrrhizins as the principal ingredient to the absorption promoter is (20:1) to (1:20), and the preferable preparation comprises 5-30wt.% glycyrrhizin, 5-30wt.% capric acid or th salt thereof, 20-50wt.% polyethylene glycol, 0-10wt.% propylene glycol, 0-10wt.% distilled water and 0-3wt.% caustic soda to provide 100wt.%. The enteric coating material is carboxymethyl ethyl cellulose, an azo polymer, etc.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

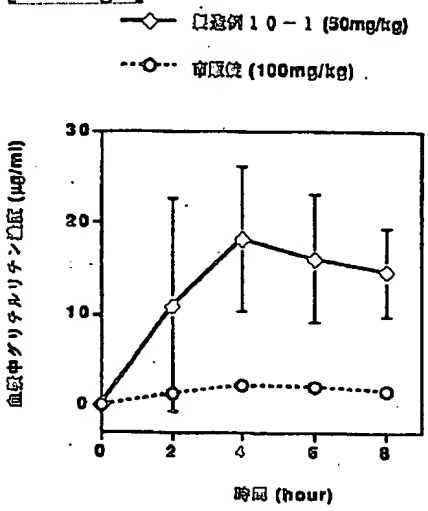
[Date of extinction of right]

* NOTICES *

1.This document has b n translated by computer. So the translation may not reflect the original pr cisely.
2.***** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DRAWINGS

[Drawing 1]



[Translation done.]

* NOTICES *

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2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] The glycyrrhizin internal use tablet characterized by solubilizing at least one sort of chief remedies and the absorption accelerator which are chosen from glycyrrhizin and its salt by the solubilizing agent, and covering with an enteric nature coat.
[Claim 2] The internal use tablet given in claim 1 term characterized by making at least one of medium chain fatty acid and the salts of its contain as an absorption accelerator.
[Claim 3] The internal use tablet given in claim dyadic given absorption accelerators are a capric acid and/or its specific salt.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect th original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention relates to the oral tablet which raised the translatability to the inside of glycyrrhizin and the blood of the salt.
[0002]
[Description of the Prior Art] Glycyrrhizin and its derivative, or those salts are independent, or it is blended with amino acid etc., and having various kinds of medicinal action, for example, an anti-cortisone operation, a ** cholesterol operation, an anti-allergy operation, an anti-inflammatory activity, a detoxifying effect, a gastric ulcer repair operation, etc. is known. Moreover, recently, a glycyrrhizin tablet is used in many cases as the tablet for the liver disease treatment, especially injection by having reported the usefulness of the extensive medication by the intravenous injection of the glycyrrhizin to chronic liver disease, or its salt (it may abbreviate to glycyrrhizin hereafter). However, since it was generally needed for liver disease to **** a medicine over a long period of time comparatively, in order that the medication method by the intravenous injection of a glycyrrhizin tablet not only gives the pain, but medication might cross it to a patient at every day and a long period of time at the time of medication, it also had the problem make the organization of an injection site produce a thickening.
[0003] Then, although it becomes the best technique of solving these troubles to consider glycyrrhizin as an oral tablet, it is reported that the guru chill ****** oral tablet of the whole body operation expectation marketed now has a problem in the translatability to the inside of blood for the metabolism by the first time transit effect in the decomposition and liver by the enzyme within an alimentary canal etc. moreover, the decomposition product produced with the enzyme within an alimentary canal etc. may cause side effects, such as false aldosteronism, — etc. — the guru chill ****** oral tablet marketed now includes the remarkable trouble
[0004] Therefore, many studies of tablet-izing made to shift into blood are performed without decomposition of glycyrrhizin within an alimentary canal by technique other than vena medication. For example, about the suppository, the following are reported as dosage forms replaced with a glycyrrhizin oral tablet.
(1) If rectum medication of the guru chill ****** is carried out, since it will be absorbed from a rectum and it will shift into blood, the possibility of a suppository is reported (refer to JP,3-2122,A).
(2) It is reported by the technique of distributing to the bases (for example, oui **********, migriol, etc.) of lipophilic property, and carrying out rectum medication of the glycyrrhizin that a conversion into the blood of glycyrrhizin is promoted (refer to JP,3-123731,A).
(3) It is reported by by blending at least one of non-ion system surfactants (for example, polyoxyethylene lauryl ether etc.) and the medium-chain-fatty-acid salts (alkali-metal salt of the fatty acid of inside chains, such as a capric acid or a caproic acid) with glycyrrhizin as an absorption accelerator that the suppository which shows the outstanding absorptivity is obtained (refer to JP,4-261117,A).
[0005] (4) It is reported by nonionic surfactants (for example, polyoxyethylene alkyl ether etc.) and by blending water-soluble carboxylic acids (a capric acid, malonic acid, etc.) and the salt of those further if needed as glycyrrhizin and an absorption accelerator that the suppository which shows the outstanding absorptivity is obtained (refer to JP,5-97680,A).
(5) It is reported by by blending absorption accelerators (for example, capric-acid sodium etc.), pH regulator (for example, sodium hydroxide), or a ********** cholic acid with glycyrrhizin that the

suppository which shows the outstanding absorptivity is obtained (refer to JP,7-82155,A).
[0006] How ver, there ar many patients who also complain long-term medication of a suppository of the dissatisfaction even if it is not comparable to the injection, and the oral tablet is too desired in long-term medication. Th n, the study of the following tablet-izing is reported about considering glycyrrhizin as an oral tablet.
(6) It is reported that the oral tablet which blends glycyrrhizin and a fatty-acid glyceride (for example, th monochrome, **, or the ******** ceride of a fatty acid of inside chains, such as stearin acid or a caprylic acid), covers with an enteric nature coat, tablet-izes, and shows the outstanding absorptivity is obtained (refer to JP,3-255037,A).
[0007] (7) glycyrrhizin — a fat emulsion or a conjugated lipid — consider as a mixture, blend an absorption accelerator (a non-ion system surfactant, medium chain fatty acid (for example, capric acid), its salts, and its glyceride) etc., and consider as xeransis powder Furthermore, it fabricates, and it covers with an enteric nature coat, and tablet-izes, and it is reported that the oral tablet which shows the absorptivity which was excellent in the small-intestine upper part is obtained (refer to JP,6-192107,A). However, these tablets do not show sufficient absorption to the inside of the body still more compared with the blood drug concentration of the injection which the effect has decided.
[0008]
[M ans for Solving the Problem] As a result of examining zealously the tablet technique of improving the absorptivity to the inside of the body in the internal use of glycyrrhizin, this invention persons Then, glycyrrhizin or its salt, As an absorption accelerator, at least one of medium chain fatty acid and the salts of its is made to contain, a pH regulator is added if needed, it solubilizes by the solubilizing agent, this is further covered with an enteric nature coat, and an oral tablet is formed, That is, it found out that th absorptivity which was extremely superior to the conventional oral tablet was shown by performing the exudation from the tablet of a chief remedy and an absorption accelerator in the alimentary canal lower part (especially intestinum crassum) in the status that it solubilized.
[0009] Generally, it was reported that the medium chain fatty acid as an absorption accelerator and the absorption facilitatory effect of the salts have the largest intestinum crassum of an alimentary canal (a d velopment "the medicine sending method" of the drug, 13, 50 -73 (1988) reference), and the technique of s nding a medicine to an intestinum crassum has been developed (refer to JP,3-7718,A). However, since an intestinum crassum is a site which absorbs moisture, moisture is not fully supplied like the alimentary canal upper part, but it has very little moisture within a normal intestinum crassum. Therefore, the improvement of sufficient absorption did not accept only by sending a solid medicine and a solid absorption accelerator simply to an intestinum crassum. Then, the solubilizing agent of this invention solves this trouble by solubilizing a solid medicine and a solid absorption accelerator.
[0010] solubilizing medium chain fatty acid and its salts as glycyrrhizin and an absorption accelerator — the conventional technique (7) — a fat emulsion or a conjugated lipid — it is thought that it was very difficult as it understands, even if it sees from considering as the mixture However, this invention persons succeeded in solubilizing by using the solubilizing agent of this invention. That is, solubilizing and forming the medium chain fatty acid and its salts as glycyrrhizin and its salt, and an absorption accelerator into an oral tablet by the solubilizing agent of this invention is finished for the first time by this invention persons.
[0011]
[Elements of the Invention] this invention solubilizes at least one sort of chief remedies and the absorption accelerator which are chosen from (1) glycyrrhizin and its salt by the solubilizing agent. The glycyrrhizin internal use tablet characterized by covering with an enteric nature coat, (2) It is related with the internal use tablet of the aforementioned (1) publication characterized by making at least one of medium chain fatty acid and the salts of its contain as an absorption accelerator, and the internal use tablet of the aforementioned (2) publication whose (3) absorption accelerators are a capric acid and/or its specific salt.
[0012] As a salt of the glycyrrhizin of a chief remedy in this invention tablet what is permitted as physic — it is — ****ing — alkali metal (a potassium —) Salts, such as sodium, the salt of alkaline earth metal (calcium, magnesium, etc.), an ammonium salt and the organic amine (tetramethylammonium —) permitted pharmacologically A triethylamine, a monomethylamine, a dimethylamine, a cyclopentyl amine, Salts, such as a benzylamine, phenethylamine, a piperidine, a monoethanolamine, a diethanolamine, a tris

(hydroxymethyl) aminomethane, a lysine, an arginine, and an N-methyl-D-glucamine, etc. are m ntioned. A glycyrrhizin disodium salt, glycyrrhizin and 2 potassium salt, or a glycyrrhizin monochrome ammonium salt is specially desirable. These are independent, or can use together and use two kinds.

[0013] As the medium chain fatty acid and its salts of the absorption accelerator in this invention tablet, the salt of those alkali m tal (a potassium, sodium, etc.), such as a capric acid, a caprylic acid, and a caproic acid, the salt of alkaline earth metal (calcium, magnesium, etc.), etc. are mentioned, for xample. Also of these, especially a capric acid or a capric-acid specific salt is desirable.

[0014] as a solubilizing agent in this invention tablet, a polyethylene glycol, for example, [polyethylene-glycol 400(registered-trademark, following, PEG400)], propylene-glycol, and nonionic-surfactant [(HCO-60), for example, hydrogenation hardening castor oil,], distilled water, etc. are mentioned, and these are independent — or it can be combined and used Especially as a solubilizing agent, the combination of PEG400, a propylene glycol, and distilled water or the combination of PEG400 and distilled water is desirable.

[0015] Although the compounding ratio with the glycyrrhizin of a chief remedy and an absorption accelerator changes with modalities of absorption accelerator, as a mole ratio, they are 20:1 - 1:20 and are 8:1-1:8 more preferably.

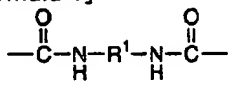
[0016] When combining desirable PEG400 and a desirable propylene glycol, and distilled water especially as a solubilizing agent, as a weight ratio, those compounding ratios are 6:1:1-1:1:1, and are 4:1:1-3:1:1 more preferably. Moreover, as a weight ratio, the compounding ratios in the case of combining PEG400 and distilled water are 6:1-1:1, and are 4:1-3:1 more preferably.

[0017] The compounding ratio of the sodium hydroxide as PEG400, the propylene glycol, distilled water, and the pH regulator as the capric acid and its salt, and solubilizing agent as the glycyrrhizin and the absorption accelerator of a chief remedy The capric acid and its salt as an absorption accelerator five to 30% of the weight 5 - 30 % of the weight, [the glycyrrhizin and its salt of a chief remedy] 0 - 3% of the w ight of composition is [a propylene glycol / distilled water / a sodium hydroxide] desirable [PEG400 / zero to 10% of the weight] zero to 10% of the weight 20 to 50% of the weight (however, the sum of all combination is 100 % of the weight.). .

[0018] As a pH regulator in this invention tablet, the hydrate of alkali metal (a potassium, sodium, etc.) or the hydrate of alkaline earth metal (calcium, magnesium, etc.) is desirable. Especially, a sodium hydroxide is desirable.

[0019] Carboxy methyl ethyl cellulose, a hydroxypropyl-methylcellulose free-wheel-plate rate, a cellulose acetate, a methacrylic-acid system copolymer, an azo polymer, etc. can be used that what is necessary is just what is usually used for a medicine as a material of the enteric nature coat in this invention tablet. What can use what is generally known, for example, was indicated by JP,3-7718,A as an azo polymer is mentioned. It is JP,3-7718,A preferably and they are the following formulas A, B, C, and D [0020].

[Formula 1]

A: 

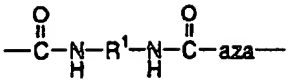
B: —aza—

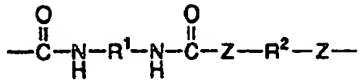
C: $Z-R^2-Z$

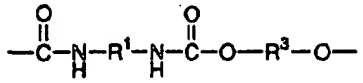
D: $—O-R^3-O—$

A-B, A-C, and A-D [0021] which it comes out of and are produced with the combination of a structural unit shown

[Formula 2]

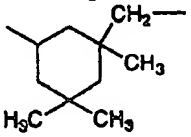
A-B: 

A-C: 

A-D: 

The azo polymer which it has ********** as a segment and segment mole-ratio x:y:z of A-B, A-C, and A-D becomes from two or more segments whose average molecular weight is 1000-100000 in 0.01-0.8:0-0.80:0-0.99 (however, it is x+y+z=1.0) [0022] The inside of [formula and R1 are a formula (1).

[Formula 3]

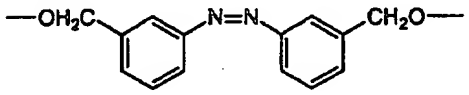


(1)

It comes out, the base shown is expressed, three R1 in each segment of A-B, A-C, and A-D expresses the same machine, and aza is a formula (2).

[0023]

[Formula 4]



(2)

It comes out, the base shown is expressed, Z-R2-Z expresses the residue of a polyethylene glycol, and R3 expresses 1 and 2-propylene.] An azo polymer given in the examples 12 and 12 of JP,3-7718,A (a) is still desirable.

[0024] As dosage forms of the oral tablet of this invention, a capsule is desirable and a soft capsule is still desirable. You may make a stabilizer, a surfactant, a diluent, an additive, lubricant, a solubilizing agent, and antiseptics contain in case of tablet-izing if needed. Although there is especially no limit and it changes with a symptom, age, etc. if the glycyrrhizin content in this invention is an amount which can discover ****, preferably, once, an amount is 1-500mg and a medicine can be prescribed for the patient 1 to several times per day.

[0025]

[Effect] At least one of medium chain fatty acid and the salts of its is made to contain as glycyrrhizin or its salt, and an absorption accelerator, and it solubilizes by the solubilizing agent, and further, by covering this with an enteric nature coat and forming it into an oral tablet, a medicine will send the alimentary canal lower part (especially intestinum crassum) by internal use, and it becomes possible to make the inside of the body absorb glycyrrhizin or its salt by high concentration. Moreover, the extensive medication from which sufficient pharmacology effect which is equal to vena medication is acquired becomes possible by internal use.

[0026]

[Example] Hereafter, although this invention is explained in full detail by the example of a manufacture, and the example of an experiment, this invention is not limited to these. The section means the weight section among the following examples.

[0027] Example [of a Manufacture] 1: The polyethylene glycol 400 and the propylene glycol were mixed by component combination of the solution prescription following, and it added gradually, ****ing glycyrrhizin and an ammonium salt. Churning mixtur was carried out and the solution was prepared until it added a capric acid and specific-salt powder to the obtained solution and it became clear.

[0028]

[Table 1]

** A part Loadings Glycyrrhizin and an ammonium salt The 30 sections A capric acid and a specific salt

The 12 s ctions propylene glycol The five sections Polyethylene glycol 400 The 53 sections A total of the 100 sections [0029] Example [of a Manufacture] 2: The polyethylene glycol 400 and the propylene glycol were mixed with th component loadings of the solution prescription following, and it added gradually, ****ing glycyrrhizin and 2 potassium salt. Churning mixture was carried out and the solution was prepared until it added a capric acid and specific-salt powder to the obtained solution and it became clear.

[0030]

[Table 2]

** A part Loadings Glycyrrhizin and 2 potassium salt The 30 sections A capric acid and a specific salt The 12 sections propylene glycol The five sections Polyethylene glycol 400 The 53 sections A total of the 100 sections [0031] Example [of a Manufacture] 3: The polyethylene glycol 400 and the propylene glycol were mixed with the component loadings of the solution prescription following, and it added gradually, ****ing a glycyrrhizin disodium salt. Churning mixture of the capric acid which carried out melting to the obtained solution was added and carried out, and the solution was prepared.

[0032]

[Table 3]

** A part Loadings A glycyrrhizin disodium salt The 30 sections A capric acid The 12 sections Propylene glycol The ten sections Polyethylene glycol 400 The 48 sections A total of the 100 sections [0033] Example [of a Manufacture] 4: The polyethylene glycol 400 was mixed in the solution which melted the sodium hydroxide in water with the component loadings of the solution prescription following, and it added gradually, ****ing glycyrrhizin and an ammonium salt. Churning mixture of the capric acid which carried out melting to the obtained solution was added and carried out, and the solution was prepared.

[0034]

[Table 4]

** A part Loadings Glycyrrhizin and an ammonium salt The 30 sections A capric acid The 15 sections Water The 8.8 sections Sodium hydroxide The 1.2 sections Polyethylene glycol 400 45 ****s The 100 s ctions [0035] Example [of a Manufacture] 5: The polyethylene glycol 400 was mixed in the solution which melted the sodium hydroxide in water with the component loadings of the solution prescription following, and it added gradually, ****ing glycyrrhizin and an ammonium salt. Churning mixture of the capric acid which carried out melting to the obtained solution was added and carried out, and the solution was prepared.

[0036]

[Table 5]

** A part Loadings Glycyrrhizin and an ammonium salt The 20 sections A capric acid The 25 sections Water The 8.3 sections Sodium hydroxide The 1.7 sections Polyethylene glycol 400 45 ****s The 100 sections [0037] Example [of a Manufacture] 6: The polyethylene glycol 400 was mixed in the solution which melted the sodium hydroxide in water with the component loadings of the solution prescription following, and it added gradually, ****ing glycyrrhizin and an ammonium salt. Churning mixture of the capric acid which carried out melting to the obtained solution was added and carried out, and the solution was prepared.

[0038]

[Table 6]

** A part Loadings Glycyrrhizin and an ammonium salt The 15 sections A capric acid The 30 sections Water The 7.7 sections Sodium hydroxide The 2.3 sections Polyethylene glycol 400 45 ****s The 100 sections [0039] The soft capsule which contains about 45mg per capsule of glycyrrhizin disodium salts for what was manufactured in the example 1 of an oral tablet manufacture of example of manufacture 7-1:solution prescription per capsule according to a conventional method was **ed, and it considered as the oral tablet.

[0040] Although manufactured in the example 1 of an oral tablet manufacture of example [of a manufacture] 7-2, - 7-6:solution prescription, by carrying out the same operation as the example 7-1 of a manufacture using what was instead manufactured in the examples 2-6 of a manufacture, it considered as the oral tablet.

[0041] Using the spray pan-coating machine, according to the conventional method, carboxy methyl ethyl cellulose was coated 10%, and the soft capsule which manufactured example of manufacture 8-

1:solution pr scription in the example 7-1 of an oral tablet manufacture coated with the enteric nature coat was consider d as the oral tablet.
[0042] Although example [of a manufacture] 8-2 - 8-6:solution prescription was manufactured in the xample 7-1 of an oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 8-1 of a manufacture using what was instead manufactured in the example 7-2 to 7-6 of a manufacture, it considered as the oral tablet.
[0043] Using the spray pan-coating machine, according to the conventional method, carboxy methyl ethyl cellulose was coated 15%, and the soft capsule which manufactured example of manufacture 9-1:solution prescription in the example 7-1 of an oral tablet manufacture coated with the enteric nature coat was considered as the oral tablet.
[0044] Although example [of a manufacture] 9-2 - 9-6:solution prescription was manufactured in the example 7-1 of an oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 8-1 of a manufacture using what was instead manufactured in the example 7-2 to 7-6 of a manufacture, it considered as the oral tablet.
[0045] According to the conventional method, the azo polymer (example 12 of JP,3-7718,A) was coated 5% using the spray pan-coating machine, and the tablet which manufactured example of manufacture 10-1:solution prescription in the example 8-1 of an oral tablet manufacture coated with the enteric nature coat was considered as the oral tablet.
[0046] Although example [of a manufacture] 10-2 - 10-6:solution prescription was manufactured in the example 8-1 of an oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 10-1 of a manufacture using what was instead manufactured in the example 8-2 to 8-6 of a manufacture, it considered as the oral tablet.
[0047] Example [of a Comparison] 1: Granulatio with a diameter of about 1mm was **ed by the conventional method with the centrifugal fluidized-bed-granulation machine which carries out the granulation of the following powder, using non ****** (refined-sugar grain, 24 - 34 meshes) 500g as an oral tablet nucleus of powder prescription, and it considered as the oral tablet. Finally, the glycyrrhizin disodium salt became 39.4% among [all] the tablet, and the capric acid and the specific salt became about 17%.
[0048]
[Table 7]
** A part Loadings A glycyrrhizin disodium salt The 53 sections A capric acid and a specific salt The 25 sections Hydroxypropylcellulose (L-HPC) The 15 sections Microcrystalline cellulose (Avicel) The seven sections A total of the 100 sections [0049] Example [of a Comparison] 2: The tablet which manufactured powder prescription in the example 1 of an oral tablet comparison coated with the enteric nature coat was coated with 10% and the azo polymer (example 12 of JP,3-7718,A) 7% with carboxy methyl ethyl cellulose according to the conventional method using the spray pan-coating machine, and was considered as the oral tablet.
[0050] Internal use was carried out by kg in 50mg /, having used ****** of the example 7-1 of a manufacture, 8-1, 9-1, 10-1, the example 1 of a comparison, and the example 2 of a comparison as the glycyrrhizin disodium salt at the beagle which abstained from food overnight [example of experiment 1], and it administered intravenously by kg in 2mg /, and collected blood from the forearm vena with time, and plasma was obtained by the conventional method. The concentration of the glycyrrhizin in this plasma was measured by the high performance chromatography, and it asked for the curvilinear inferior-surface-of-tongue product (AUC and mg and min/ml) from 0 hour to [from the obtained concentration in plasma] 8 hours. The utilization factor was computed by the comparison with intravenous administration. The result is shown in Table 1. Moreover, internal use of the glycyrrhizin oral tablet (100mg/(kg)) marketed the example 10-1 (50mg/(kg)) of a manufacture and now is carried out to a beagle (3-6 animals), and the result which investigated concentration (average ** deflection) transition of the glycyrrhizin in plasma with time is shown in drawing 1 .
[0051]
[Table 8]
Table 1 Medication site Dose AUC (mg and min/ml) Utilization factor The aqueous solution The vena 2mg/kg 3408. 0 100% A commercial lock Taking orally 100mg/kg 310.2 0.2% The example 1 of a comparison Taking orally 50mg/kg 653.4 0.8% Example of comparison 2 taking orally 50mg/kg 1202. 0

1.4% The xample 7-1 of a manufactur Taking orally 50mg/kg 2010. 0 2.4% Example 8-1 of a manufacture Taking orally 50mg/kg 3378.0 4.0% Example 9-1 of a manufacture Taking orally 50mg/kg 4656.2 Example 10-1 of 5.5% manufacture Taking orally 50mg/kg 5140.5 6.0% [0052] Consideration: The tablet of this invention showed the absorptivity which was extrem ly superior to the above-mentioned result compared with th oral tablet (example 2 of a comparison) which coated a commercial oral tablet, th oral tablet (example 1 of a comparison) of powder prescription, and powder prescription with the enteric nature coat. By this, it was enabled to improve the absorptivity to the inside of the body in the internal use of glycyrrhizin and its salt.

[Translation done.]

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添付公開書類
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(54)Title: **ORAL DRUG DELIVERY SYSTEM FOR ENHANCING THE BIOAVAILABILITY OF ACTIVATED GLYCYRRHETIN**

(54)発明の名称 活性型グリチルリチンのバイオアベイラビリティを高めるための経口投与用薬物送達システム

(57) Abstract

A drug delivery system for enhancing the bioavailability of glycyrrhetin having been orally administered. This drug delivery system is one aiming at delivering oral drugs to the large intestine which comprises glycyrrhetin in an amount sufficient for selectively releasing glycyrrhetin in the large intestine at a high concentration exceeding the speed of the hydrolysis of glycyrrhetin by the intestinal flora and pharmaceutically acceptable carrier(s). It is preferable that the carriers partly or totally comprise sorbefacient(s) selected from the group consisting of pharmaceutically acceptable organic acids, surfactants and chelating agents.

(57)要約

経口投与されたグリチルリチンのバイオアベイラビリティを増大する薬物送達システムが開示される。該薬物送達システムは、大腸内においてグリチルリチンを腸内細菌叢によるその加水分解速度を上廻る高い濃度で選択的に放出するのに十分な量のグリチルリチンと、製剤学的に許容し得る担体を含んでいる経口投与用大腸ターゲティング薬物送達システムよりなる。好ましくは担体の一部又は全部は製剤学的に許容し得る有機酸、界面活性剤およびキレート剤からなる群より選ばれた吸収促進剤である。

明　細　書

活性型グリチルリチンのバイオアベイラビリティを高めるための経口投与用薬物送達システム

本発明の背景

本発明は、グリチルリチンを経口投与するための薬物送達システム、詳しくは活性型グリチルリチンのバイオアベイラビリティを高めるためのそのような薬物送達システムに関する。

グリチルリチンは、古くから漢方薬として使用されている甘草に含まれる天然物質であり、強い甘味を呈する。甘味剤として使用されるほか、その静脈内投与により慢性肝炎、アレルギー疾患などの治療に使用されている。

グリチルリチンは化学的には2分子のグルクロン酸とグリチルレチン酸からなるグルクロナイドである。ヒトおよび動物における経口投与されたグリチルリチンの薬物動態学的挙動の研究によると、投与後血中にはグリチルレチンは殆ど検出されず、その分解産物であるグリチルレチン酸が検出されることが報告されている。例えばZhao Wang et al., Biol. Pharm, Bull. 17(10):1399-1403(1994);Y. Yamamura et al., 同誌18(2):337-341(1995);S. Takeda et al., J. Pharm. Pharmcol. 1996, 48:902-905参照。

このことからグリチルリチンはそのままの形（活性型）では消化管から殆ど吸収されず、消化管内で肝炎に対して治療効果が殆どな

いグリチルレチン酸へ加水分解され、その形で吸収されるものと考えられている。このようにグリチルリチンの経口投与によるバイオアベイラビリティーは極めて低い。

グリチルリチンのバイオアベラビリティーを改善する目的で坐剤による直腸内投与が検討されている（特開平１－２９４６１９、特開平３－２１２２および特開平３－１２３７３１）。

また消化管からの吸収を高めるため脂肪酸グリセライドの配合とエンテリックコーティングを施した経口剤（特開平３－２５５０３７）、脂肪乳剤又は複合脂質混合体を配合した経口剤（特開平６－１９２１０７）なども提案されている。しかしこれら従来の坐剤や経口剤によってもなおグリチルリチンの薬効が充分に発揮されるに足る血中濃度は得られていない。

従って、経口投与による活性型グリチルリチンのバイオアベイラビリティーを治療上有効なレベルまで高める方法およびデバイスに対する要望がなお存在する。

本発明の概要

上記要望は、本発明に従い、大腸内においてグリチルレチンを腸内細菌叢によるその加水分解速度を上廻る濃度で選択的に放出するのに十分な量のグリチルリチンを製剤学的に許容し得る担体と共に含んでいる経口投与用大腸ターゲティング薬物送達システムを提供することによって満たされる。

好ましくは、本発明の薬物送達システムは放出されたグリチルリチンの吸収を促進するため、担体の一部又は全部が吸収促進剤であることができる。

グリチルリチンをこの形の経口ＤＤＳに加工することにより、投

与されたグリチルリチンは選択的に大腸において高濃度で放出され、そのため腸内細菌叢による加水分解速度を飽和せしめ、大部分が活性体の形で大腸から吸収され、活性体であるグリチルリチンそのもののバイオアベイラビリティが著しく改善される。

本発明の薬物送達システムは、基本的にはグリチルリチンと担体を含んでいる粉末、顆粒、錠剤、丸剤、坐剤、液剤などの形の内側部分と、これを包囲するスキンもしくはシエルとからなる。このスキンもしくはシエルが大腸において選択的に溶解もしくは破れることによって内側部分が放出され、それに含まれるグリチルリチンが大腸壁から吸収される。

内側部分は腸内細菌叢による加水分解を補償する量を実質的に上廻る量のグリチルリチンを含んでいる。ここでいうグリチルリチンとは遊離のグリチルリチンのみならず、ナトリウム塩、カリウム塩またはアンモニウム塩のようなその塩を含んでいる。

好ましくは担体の一部又は全部はグリチルリチンの吸収を促進する物質である。そのような吸収促進剤は、クエン酸、リンゴ酸、マレイン酸、フマル酸、酒石酸などの製剤学上許容される有機酸類、ラウリル硫酸ナトリウム、ポリオキシエチレンソルビタン、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレンアルキルエーテル、ポリオキシエチレンアルキルフェニルエーテル、デオキシコール酸塩、ウルソデオキシコール酸塩などの製剤学上許容される界面活性剤、およびＥＤＴＡなどのキレート化剤である。

内側部分は公知の技術を用いて慣用の経口投与製剤に加工される。

経口投与用の固形製剤が胃から排出され、小腸を通って大腸に到

達するまでの時間（小腸通過時間）は約３～４時間であることが知られている。これに対し該製剤の投与後胃から排出されるまでの時間は大幅に変動する。また、消化管内ｐＨは胃において約１～３から小腸において約６～７へ明確に上昇することは周知である。これらの生理学的現象を利用して大腸ターゲティングＤＤＳを設計することが可能である。

以下、本発明に使用する大腸ターゲティングＤＤＳについて説明する。

１．　直腸投与用の坐剤に類似のグリチルリチン含有製剤をアニオン性ポリマー製のカプセルに充塡する方法

先に述べたように、カプセル、錠剤等の固形製剤の小腸通過時間は約３～４時間と比較的安定している。従ってこの通過時間内に徐々に溶解し、その終期において崩壊し、小腸下部において薬物を放出するのに必要にして十分なカプセル膜厚はインビトロ試験等によって容易に決定し得る。

このためカプセル材料として使用し得る市販のアニオン性（腸溶性）アクリルポリマーとしては、オイドラギッドＳ－１００（メタクリル酸－メタクリル酸メチルコポリマー）およびオイドラギッドアニオン性ポリマー４１３５Ｆ（メタクリル酸－アクリル酸メチル－メタクリル酸メチルコポリマー）などがある。

先に述べたように、カプセルの崩壊によりグリチルリチンが高濃度で大腸へ放出されなければならないので、カプセル中味は直腸投与用の坐剤に類似した製剤がこの目的に適している。このような製剤のつくり方は当業者には良く知られており、適当な基材例えばＷｉｔｅｐｓｏｌ　Ｈ１５（Ｄｙｎａｍｉｔ　Ｎｏｂｅｌ社製高級脂

肪酸ジー，トリグリセリド）を溶融し、グリチルリチンをそれへ添加してサスペンジョンをつくり、次に鋳型へ流し込み、固化してつくられる。この製剤を次に前記カプセルに充塡し、継目を同じポリマーによりシールする。代りに、坐剤類似の製剤の表面にディップ法により所望の膜厚のコーティング層を形成し、カプセル化してもよい。

2．　胃排出後の大腸到達時間（小腸通過）に相当する時間で放出する時間制御型カプセルに腸溶性コーティングを施す方法

この方法でつくったカプセルはＣＴＤＣ（ｃｏｌｏｎ　ｔａｒｇｅｔｅｄ　ｄｅｌｉｖｅｒｙ　ｃａｐｓｕｌｅ）として知られている。例えば高橋，医薬ジャーナルＶｏｌ．３４，Ｓ１，１９９８，２３８－２４２参照。

ＣＴＤＣの製剤学的特徴は、通常のゼラチン硬カプセルの中に薬物と共に有機酸がｐＨ調整剤として配合され、カプセルの外側を胃溶性皮膜層、水溶性皮膜層、腸溶性皮膜層の順に多層コーティングされていることである。特開平９－８７１６９に開示されている消化管下部放出型被覆カプセル製剤もこのタイプに入る。

本発明の場合、薬物はグリチルリチンであり、有機酸はクエン酸、リンゴ酸、マレイン酸、フマル酸、酒石酸等の固体の製剤学上許容される有機酸を使用する。

3．　Ｐｕｌｓｉｎｃａｐを用いる方法

この方法は、Ｃ．Ｇ．Ｗｉｌｓｏｎ　ｅｔ　ａｌ．，Ｄｒｕｇ　Ｄｅｌｉｖｅｒｙ，４：２０１－２０６（１９９７）に記載されている。この大腸デリバリシステムは、胴が水不溶性材料例えば低密度ポリエチレン製であり、キャップが通常のゼラチン製であるカプ

セルを使用する。通常のゼラチン製胴にエチルセルロースをコーティングして用いても良い。

この水不溶性カプセル胴に栓体を収容する空間を残して賦形剤と共に薬物を充塡する。次に吸水により膨張するヒドロゲル、例えば架橋ポリエチレングリコールでつくった栓体を開口部から胴内へ挿入してネックを密閉し、次いでゼラチンキャップを嵌合し、継目を適当なコーティング液によってシールすることによってつくられる。

このカプセルは、経口投与後キャップが胃液により溶解し、栓体が露出した胴が胃から小腸へ排出される。小腸を通過する間にヒドロゲル製栓体が吸水して次第に膨張し、ある時点でネックから押し出され、カプセル内味が消化管内に放出される。

栓体が胴キャップから押し出される時間は、栓体の寸法の調節によってコントロールすることができる。

4． 錠剤を大腸溶解性ポリマーでコーティングするか、または大腸溶解性ポリマー製のカプセルへ薬物を充塡する方法

大腸内細菌叢はアゾ基を還元分裂するアゾ還元酵素を分泌することが知られている。このため、アゾ基を含有するポリマー（アゾポリマー）は大腸内で特異的に分解（解重合）される。この現象を利用し、アゾポリマーで錠剤をコーティングすることにより、またはアゾポリマーを材料とするカプセルに薬物を充塡することにより、大腸ターゲティングＤＤＳを設計することができる。

種々のアゾポリマーが既に知られているが、スチレン－ヒドロキシエチルメタクリレート－ジビニルアゾベンゼン共重合体がその一例である。

アゾポリマー以外の大腸溶解性ポリマーも知られている。その一例は高田らにより、ＰＨＡＲＭＡ　ＴＥＣＨ　ＪＡＰＡＮ，Ｖｏｌ．１１（１１），３７－４６（１９９５）に開示されているセロビオースとポリテトラメチレングリコールをテレフタル酸とのエステル結合によって連結した一種のポリエステル（ＣＴＰＴポリマー）である。

５．　放出時間制御型大腸デリバリカプセルによる方法

この方法は、高田の米国特許第５，６３７，３１９号に第１法として開示されている。その概要は、エチルセルロース製のカプセルを使用し、薬物のほかに、カプセル内へ充填した水膨潤性物質の膨潤圧によって投与後所定時間経過した時カプセルを破裂させ、薬物を放出するシステムである。

膨潤性物質としては、低置換度ヒドロキシプロピルセルロース（Ｌ－ＨＰＣ）、ＣＭＣナトリウム、ＣＭＣカルシウムなどを使用することができる。膨潤性物質は例えば錠剤のようなカプセル内にフィットする形状の塊に成形して適当な位置に充填し、残りのスペースに薬物、この場合はグリチルリチンを賦形剤もしくは担体と混合して充填する。膨潤性物質が対面するカプセル壁には水分が浸透し得る細孔を適当な個所に設けるほかは、カプセルは密封される。

このカプセルを経口投与する時、細孔から浸透した水分により次第に膨潤する塊の膨潤圧力により、一定期間経過後カプセルが破裂し、収容されている薬物を放出する。細孔の数および孔径、カプセル膜厚、膨潤性物質の種類および寸法を適宜選択することにより、破裂までの時間を大腸放出型とするのに必要な時間に制御することができる。

6． 大腸内圧崩壊型デリバリーカプセルによる方法

この方法は、高田の米国特許第５，６３７，３１９号に第２法として記載され、また、製剤と機械、平成１０年１月１５日号にも記載されている。

このカプセルは以下の原理によって大腸で崩壊する。摂取した食物は胃および小腸内では消化液などの水分が豊富なため流動性であるが、大腸内では水分の再吸収および糞便の形成が起こるため内容物の粘度が著しく上昇している。このような高密度環境にあるカプセルは大腸の蠕動運動により派生する大腸管腔内圧によって破裂し、中味の薬物を放出する。

このカプセルはエチルセルロース膜でつくった、または該膜で内張りしたゼラチンカプセルである。

カプセル中味はカプセル圧潰時液状でなければならないから、グリチルリチンはプロピレングリコール、ポリエチレングリコール、植物油、または体温において液化する坐剤の基剤に溶解または分散してカプセル収容される。

エチルセルロースカプセルの膜厚を変えることにより、カプセルの大腸内崩壊時間を制御することができる。

上で引用したすべての特許及び文献の記載を参照としてここに取り入れる。

本発明のグリチルリチン製剤の適応疾患としては、慢性肝疾患における肝機能異常、各種湿疹、薬疹、口内炎、小児ストロフィス、フリクテン、円形脱毛症などがあげられる。

本発明のグリチルリチン製剤の投与量は、患者の年齢、体重、疾病の種類や進行状況等を考慮して決定すればよいが、肝疾患の治療

に対しては成人（体重６０ｋｇとして）１日当たり、グリチルリチンとして１０～１，０００ｍｇ、好ましくは１００～８００ｍｇ程度である。この投与量は１回または数回に分けてすることができる。

本発明の限定を意図しない以下の実施例によってさらに詳しく説明される。

実施例１

グリチルリチンナトリウム塩１００ｍｇをプロピレングリコール０．５ｍＬに溶解し、ＨＣＯ－６０（ポリオキシエチレン硬化ヒマシ油）１００ｍｇを添加して液剤とし、大腸内圧崩壊型大腸デリバリカプセル（ゼラチンカプセルの内側にエチルセルロース膜をライニングしたもの）へ充填する。

実施例２

グリチルリチンカリウム塩１００ｍｇを５０℃に加熱したＷｉｔｅｐｓｏｌ　Ｈ１５（高級脂肪酸ジー，トリグリセリド）４００ｍｇに分散し、鋳型へ注ぎ込み、冷却、固化して坐剤様成形体を得る。この成形体を６℃に冷却し十分に固化させた後、精製タルクを薄くまぶし、ディッピング法によりエチルセルロースフィルムでコーティングし、大腸内圧崩壊型大腸デリバリカプセルを得る。

実施例３

Ｐｕｌｓｉｎｃａｐ（英国Ｓｃｈｅｒｅｒ　ＤＤＳ　Ｌｔｄ．製）にグリチルリチンナトリウム１００ｍｇを充填する。

実施例４

グリチルリチンナトリウム１００ｍｇを用いて常法により錠剤を調製し、大腸溶解性ＣＴＰＴポリマーにてコーティングを施し、大

腸ターゲティングＤＤＳを得る。

インビボバイオアベイラビリティ試験

方法：

前日夜から１２時間の絶食を行ったビーグル犬に、５０ｍＬの水とともに試験製剤を経口投与し、２４時間にわたって頸動脈より血液サンプル２ｍＬを採取し、血漿中のグリチルリチン濃度をＨＰＬＣ法によって測定した。対照として市販のグリチルリチン錠（グリチロン錠）を用いた。なお、投与量は１００ｍｇである。

試験結果：

血漿グリチルリチン濃度（μｇ／ｍＬ）

	投与後経過時間（ｈｒ）				
	1	2	3	4	5
グリチロン錠	ＮＤ	ＮＤ	ＮＤ	ＮＤ	ＮＤ
実施例２製剤	ＮＤ	ＮＤ	0．7	4．8	5．9

	6	8	10	24
グリチロン錠	ＮＤ	ＮＤ	ＮＤ	ＮＤ
実施例２製剤	4．7	3．7	3．1	2．9

表に示されているように、市販のグリチルリチン錠の経口投与では血漿中にグリチルリチンが検出されなかったが、大腸ＤＤＳカプセルとして実施例2の製剤の経口投与では投与3時間後から血漿中のグリチルリチン濃度が上昇し始め、４～５時間でピークに達し、少なくとも２４時間治療有効濃度が持続する。

請　求　の　範　囲

1．　大腸内においてグリチルリチンを腸内細菌叢によるその加水分解速度を上廻る高い濃度で選択的に放出するのに十分な量のグリチルリチンを製剤学的に許容し得る担体と共に含んでいる経口投与用大腸ターゲティング薬物送達システム。

2．　担体の一部又は全部が製剤学的に許容し得る有機酸、界面活性剤およびキレート化剤からなる群から選ばれた吸収促進剤である請求項1の薬物送達システム。

3．　グリチルリチンを含んでいる坐剤をアニオン性ポリマー製カプセルに収容してなる請求項1又は2の薬物送達システム。

4．　外側を胃溶性皮膜、水溶性皮膜および腸溶性皮膜の順に多層コーティングされているゼラチンカプセルにグリチルリチンと共に有機酸が充塡されている請求項1又は2の薬物送達システム。

5．　開口部をヒドロゲル栓体で閉鎖した水不透性カプセル胴内にグリチルリチンと担体の混合物が充塡され、カプセル胴は水溶性カプセルキャップで蓋をされている請求項1又は2の薬物送達システム。

6．　大腸溶解性ポリマーでコーティングされているグリチルリチン含有錠剤である請求項1又は2の薬物送達システム。

7．　大腸溶解性ポリマー製カプセルにグリチルリチンが担体と共に充塡されている請求項1又は2の薬物送達システム。

8．　カプセル壁の一部分の区域に設けた細孔を有するエチルセルロース製カプセル内に該孔に対面して水膨潤性物質の塊が充塡され、残りのスペースにグリチルリチンおよび担体が充塡されている

請求項１又は２の薬物送達システム。

９．グリチルリチンを大腸ターゲティング薬物送達システムを使ってヒトに経口投与し、そして大腸内において選択的に放出せしめることを含む経口投与されたグリチルリチンのバイオアベイラビリティを増加させる方法。

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 May 2000 (02.05.00)	
International application No. PCT/JP99/05153	**Applicant's or agent's file reference** FP319
International filing date (day/month/year) 20 September 1999 (20.09.99)	**Priority date** (day/month/year) 21 September 1998 (21.09.98)
Applicant TAKADA, Kanji	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

07 April 2000 (07.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Diana Nissen
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Translation

PATENT COOPERATION TREATY 09/787612

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FP319	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP99/05153	International filing date (*day/month/year*) 20 September 1999 (20.09.99)	Priority date (*day/month/year*) 21 September 1998 (21.09.98)
International Patent Classification (IPC) or national classification and IPC A61K 31/70, 9/00, 9/48		
Applicant AMATO PHARMACEUTICAL PRODUCTS, LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 April 2000 (07.04.00)	24 August 2000 (24.08.2000)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP99/05153

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP99/05153

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 9

because:

☒ the said international application, or the said claims Nos. 9
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

The subject matter of Claim 9 relates to a method for treatment of the human body by therapy or surgery, which does not require an international preliminary examination by the International Preliminary Examining Authority.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 9 .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP99/05153

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-8	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations

(Documents)

1. JP, 6-192107, A (Sanwa Kagaku Kenkyusho Co., Ltd.) (12.07.94)
2. JP, 10-226650, A (Ono Pharmaceutical Co., Ltd.) (25.08.98)
3. JP, 3-255037, A (Santen Pharmaceutical Co., Ltd.) (13.11.91)
4. JP, 58-501174, A (Tillotts Pharma. AG) (21.07.83)
5. JP, 9-87169, A (Tanabe Seiyaku Co., Ltd.) (31.03.97)
6. Journal of Medicine, Vol. 34, S-1 (01.01.98), pages 237 to 242
7. Drug Delivery, Vol. 4, No. 3, 1997, pages 201 to 206
8. Pharm Tech Japan, Vol. 11, No. 11, 1995, pages 37 to 46
9. WO, 94/10983, A1 (Hisamitsu Pharmaceutical Co., Inc.) (26.05.94)
10. JP, 8-253413, A (Kanji Takada) (01.10.96)

(Commentary)

Claims 1-8

Documents 1-3 cited in the international search report describe drug preparations with glycyrrhetin as their main ingredient and oral drug preparations that are absorbed in the intestine such as the large intestine and the like in order to increase the absorption of glycyrrhetin.

As described in documents 4-10, in this field of technology the selective absorption of a drug in the large intestine in order to increase the absorption of the main ingredient is widely known. In addition, to achieve this purpose document 4 describes an oral preparation in which the main ingredient is coated with an anionic polymer. Documents 5 and 6 describe oral preparations in which the main ingredient is packed together with an organic acid in a gelatin capsule that has been coated in multiple layers successively with a film that dissolves in the stomach, a film that is water soluble, and a film that dissolves in the intestine. Document 7 describes an oral preparation in which a non-water-permeable capsule body with an orifice that is sealed with a hydrogel plug is packed with the main ingredient and a carrier and then enclosed in a water-soluble capsule cap. Documents 8 and 9 describe oral preparations in which a tablet containing the main ingredient is coated with a polymer that dissolves in the large intestine. Document 10 describes an oral preparation in which a gel material, the main ingredient, and a vehicle are packed in a capsule made of a polymer that dissolves in the large intestine and has fine pores.

Therefore, persons skilled in the art can easily utilize any of these preparations as a preparation in which the main ingredient is glycyrrhetin.

As a result, the subject matter of Claims 1-8 does appear to be novel but does not appear to involve an inventive step.

(54) ORAL THROMBIN PHARMACEUTICAL PREPARATION
(11) 3-255035 (A) (43) 13.11.1991 (19) JP
(21) Appl. No. 2-50494 (22) 1.3.1990
(71) MOCHIDA PHARMACEUT CO LTD (72) YASUYUKI KUNIHIRO(3)
(51) Int. Cl⁵. A61K37/54,A61K9/14,A61K9/16,A61K37/54,A61K47/26,A61K47/42

PURPOSE: To obtain the title pharmaceutical preparation each containing thrombin as hemostatic ingredient, gelatin, etc., as a stabilizer and white sugar, etc., as a vehicle, being stable for a long period at ambient temperature, having excellent solubility and usable as a form of powder, fine grain, granule, etc., and suitable for treatment of bleeding from upper digestive tract.

CONSTITUTION: In the title pharmaceutical preparation, a stabilizer (e.g. gelatin, albumin or glycine) of 10-50mg and a vehicle (e.g. white sugar, lactose or D-mannitol) of 0.5-1g per 10000 unit thrombin are blended. The above-mentioned preparation is used by dissolving the preparation in to buffer, cow milk, physiological saline, distilled water, etc., and controlling the concentration of thrombin to 50-100unit/m*l*. The preparation is dissolved within 1 min in a solvent and the solution is free from precipitation. Further, thrombin activity in the solution is not lowered for 24hr.

(54) METHOD FOR STABILIZING KALLIKREIN
(11) 3-255036 (A) (43) 13.11.1991 (19) JP
(21) Appl. No. 1-103783 (22) 24.4.1989
(71) SHUNICHI NAITO (72) SHUNICHI NAITO
(51) Int. Cl⁵. A61K37/553,A61K47/22,A61K47/26,A61K47/36,A61K47/42

PURPOSE: To stabilize kallidinogenase preparation useful as a improver for hindrance of circulation by blending kallidinogenase with adenine and preferably further albumin, mannite and/or chondroitin sufluric acid.

CONSTITUTION: Kallidinogenase preparation, especially kept in contact state with water is stabilized by blending kallidinogenase with adenine and further, as necessary, albumin, mannite and/or chondroitin sulfuric acid. Since kallidinogenase is unstable by heating, acid, or alkali, it was required to prepare solution thereof just before use, especially in the case of an aqueous solution such as injection. But, solution thereof can be stabilized by the above-mentioned method. The taking case of purity, origin, etc., of kallidinogenase, adenine, albumin, etc., is unnecessary. The kallidinogenase is effective on the improvement of peripheral circulation hindrance such as hypertension or Meniere's syndrome.

(54) GLYCYRRHIZIN PHARMACEUTICAL PREPARATION
(11) 3-255037 (A) (43) 13.11.1991 (19) JP
(21) Appl. No. 2-52350 (22) 2.3.1990
(71) SANTEN PHARMACEUT CO LTD (72) TAKAKAZU MORITA(2)
(51) Int. Cl⁵. A61K47/14,A61K9/48,A61K9/52,A61K31/70

PURPOSE: To obtain a glycyrrhizin preparation capable of quickly increasing the concentration of glycyrrhizin in blood by blending glycyrrhizin or salt thereof with a fatty acid glyceride and coating the blend with an enteric coating film.

CONSTITUTION: Glycyrrhizin or salts thereof is blended with a fatty acid glyceride (e.g. mono, di or triglyceride of middle chain fatty acid such as stearic acid or caprylic acid) at a ratio of (1:1)-(1:10.0) and the blend is coated with an enteric coating film (e.g. hydroxypropylmethylcellulose phthalate) to provide a glycyrrhizin preparation having a form of tablet, granule, inhalant, capsule, etc. When the preparation is administered, glycyrrhizin is rapidly absorbed in the duodenum or small intestine, because the enteric coating film is dissolved in the duodenum and moved into blood to effectively exhibit the effect. Glycyrrhizin is effective in the therapy of liver disease, allergic disease, etc.

特　許　協　力　条　約

09/787612

EP　US　PCT

国際調査報告

（法８条、法施行規則第40、41条）
〔ＰＣＴ１８条、ＰＣＴ規則43、44〕

出願人又は代理人の書類記号　ＦＰ３１９	今後の手続きについては、国際調査報告の送付通知様式（ＰＣＴ／ＩＳＡ／２２０）及び下記５を参照すること。	
国際出願番号 ＰＣＴ／ＪＰ９９／０５１５３	国際出願日 （日.月.年）　２０．０９．９９	優先日 （日.月.年）　２１．０９．９８
出願人（氏名又は名称） 天藤製薬株式会社		

国際調査機関が作成したこの国際調査報告を法施行規則第41条（ＰＣＴ１８条）の規定に従い出願人に送付する。
この写しは国際事務局にも送付される。

この国際調査報告は、全部で　4　ページである。

☐ この調査報告に引用された先行技術文献の写しも添付されている。

１．国際調査報告の基礎

ａ．言語は、下記に示す場合を除くほか、この国際出願がされたものに基づき国際調査を行った。
☐ この国際調査機関に提出された国際出願の翻訳文に基づき国際調査を行った。

ｂ．この国際出願は、ヌクレオチド又はアミノ酸配列を含んでおり、次の配列表に基づき国際調査を行った。
☐ この国際出願に含まれる書面による配列表
☐ この国際出願と共に提出されたフレキシブルディスクによる配列表
☐ 出願後に、この国際調査機関に提出された書面による配列表
☐ 出願後に、この国際調査機関に提出されたフレキシブルディスクによる配列表
☐ 出願後に提出した書面による配列表が出願時における国際出願の開示の範囲を超える事項を含まない旨の陳述書の提出があった。
☐ 書面による配列表に記載した配列とフレキシブルディスクによる配列表に記録した配列が同一である旨の陳述書の提出があった。

２．☐ 請求の範囲の一部の調査ができない（第Ⅰ欄参照）。

３．☐ 発明の単一性が欠如している（第Ⅱ欄参照）。

４．発明の名称は
☐ 出願人が提出したものを承認する。
☒ 次に示すように国際調査機関が作成した。
活性型グリチルリチンのバイオアベイラビリティを高めるための経口投与用薬物送達システム

５．要約は
☒ 出願人が提出したものを承認する。
☐ 第Ⅲ欄に示されているように、法施行規則第47条（ＰＣＴ規則38.2(b)）の規定により国際調査機関が作成した。出願人は、この国際調査報告の発送の日から１カ月以内にこの国際調査機関に意見を提出することができる。

６．要約書とともに公表される図は、
第＿＿＿＿図とする。☐ 出願人が示したとおりである。　☒ なし
☐ 出願人は図を示さなかった。
☐ 本図は発明の特徴を一層よく表している。

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ９９／０５１５３

第Ⅰ欄　請求の範囲の一部の調査ができないときの意見（第１ページの２の続き）

法第８条第３項（ＰＣＴ１７条(2)(a)）の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1．[X] 請求の範囲 9 は、この国際調査機関が調査をすることを要しない対象に係るものである。
つまり、
請求の範囲９は、人の手術又は治療による処置方法に関するものである。

2．[ ] 請求の範囲 _____ は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、

3．[ ] 請求の範囲 _____ は、従属請求の範囲であってＰＣＴ規則6.4(a)の第２文及び第３文の規定に従って記載されていない。

第Ⅱ欄　発明の単一性が欠如しているときの意見（第１ページの３の続き）

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

1．[ ] 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。

2．[ ] 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。

3．[ ] 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったので、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。

4．[ ] 出願人が必要な追加調査手数料を期間内に納付しなかったので、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意
[ ] 追加調査手数料の納付と共に出願人から異議申立てがあった。
[ ] 追加調査手数料の納付と共に出願人から異議申立てがなかった。

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ９９／０５１５３

Ａ．　発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int.Cl[6]　A61K31/70, A61K9/00, A61K9/48

Ｂ．　調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int.Cl[6]　A61K31/70, A61K9/00, A61K9/48

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

ＣＡ（ＳＴＮ）

Ｃ．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
Ｙ	ＪＰ，６－１９２１０７，Ａ（株式会社三和化学研究所），１２．７月．１９９４（１２．０７．９４），特に特許請求の範囲（ファミリーなし）	１－８
Ｙ	ＪＰ，１０－２２６６５０，Ａ（小野薬品工業株式会社），２５．８月．１９９８（２５．０８．９８），特に特許請求の範囲（ファミリーなし）	１－８
Ｙ	ＪＰ，３－２５５０３７，Ａ（参天製薬株式会社），１３．１１月．１９９１（１３．１１．９１），特に特許請求の範囲（ファミリーなし）	１－８

☒ Ｃ欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「Ａ」特に関連のある文献ではなく、一般的技術水準を示すもの
「Ｅ」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「Ｌ」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「Ｏ」口頭による開示、使用、展示等に言及する文献
「Ｐ」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「Ｔ」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「Ｘ」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Ｙ」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「＆」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
１０．１２．９９	21.12.99

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）	
日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	上條　のぶよ	４Ｃ　９４５４
	電話番号　０３－３５８１－１１０１　内線　３４５０	

様式ＰＣＴ／ＩＳＡ／２１０（第２ページ）（１９９８年７月）

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ９９／０５１５３

Ｃ（続き）．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
Ｙ	ＪＰ，５８－５０１１７４，Ａ（ジェー・ビー・ティロット・リミテッド），２１．７月．１９８３（２１．０７．８３），特に特許請求の範囲 ＆　ＥＰ，９７６５１，Ａ１　＆　ＧＢ，２１２３６９５，Ａ　＆　ＵＳ，５５４１１７１，Ａ　＆　ＵＳ，５５４１１７０，Ａ	１－３
Ｙ	ＪＰ，９－８７１６９，Ａ（田辺製薬株式会社），３１．３月．１９９７（３１．０３．９７），特に特許請求の範囲 ＆　ＥＰ，７５４５２，Ａ２	１，２，４
Ｙ	高橋保志，「最近の Drug Delivery System の進歩」，医薬ジャーナル，Vol.34，S-1，１．１月．１９９８（０１．０１．９８），ｐ．２３７－２４２	１，２，４
Ｙ	Wilson，Clive G. et.al，'Evaluation of a gastro-resistant pulsed release delivery system (Pulsincap) in humans'，Drug Delivery，Vol.4，No.3，(1997)，ｐ．２０１－２０６	１，２，５
Ｙ	増田茂樹，高田寛治，「最新の薬物大腸デリバリー技術」，PHARM TECH JAPAN，Vol.11，No.11，(1995)，ｐ．３７－４６	１，２，６
Ｙ	ＷＯ，９４／１０９８３，Ａ１（久光製薬株式会社），２６．５月．１９９４（２６．０５．９４），特に特許請求の範囲 ＆　ＵＳ，５６５４００４，Ａ　＆　ＥＰ，６６７１４８，Ａ１	１，２，６
Ｙ	ＪＰ，８－２５３４１３，Ａ（高田寛治），１．１０月．１９９６（０１．１０．９６），特に特許請求の範囲 ＆　ＵＳ，５６３７３１９，Ａ	１，２，７，８

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特　許　協　力　条　約

PCT

国際予備審査報告

（法第１２条、法施行規則第56条）
〔ＰＣＴ３６条及びＰＣＴ規則70〕

出願人又は代理人の書類記号　ＦＰ３１９	今後の手続きについては、国際予備審査報告の送付通知（様式ＰＣＴ／ＩＰＥＡ／４１６）を参照すること。	
国際出願番号 ＰＣＴ／Ｊ Ｐ９９／０５１５３	国際出願日（日.月.年）　２０．０９．９９	優先日（日.月.年）　２１．０９．９８
国際特許分類（ＩＰＣ）　Ｉｎｔ．Ｃｌ’　Ａ６１Ｋ３１／７０，Ａ６１Ｋ９／００，Ａ６１Ｋ９／４８		
出願人（氏名又は名称）　天藤製薬株式会社		

１．　国際予備審査機関が作成したこの国際予備審査報告を法施行規則第57条（ＰＣＴ３６条）の規定に従い送付する。

２．　この国際予備審査報告は、この表紙を含めて全部で　4　ページからなる。

☐　この国際予備審査報告には、附属書類、つまり補正されて、この報告の基礎とされた及び／又はこの国際予備審査機関に対してした訂正を含む明細書、請求の範囲及び／又は図面も添付されている。
（ＰＣＴ規則70.16及びＰＣＴ実施細則第６０７号参照）
この附属書類は、全部で＿＿＿＿＿＿ページである。

３．　この国際予備審査報告は、次の内容を含む。

I　☒　国際予備審査報告の基礎

II　☐　優先権

III　☒　新規性、進歩性又は産業上の利用可能性についての国際予備審査報告の不作成

IV　☐　発明の単一性の欠如

V　☒　ＰＣＴ３５条(2)に規定する新規性、進歩性又は産業上の利用可能性についての見解、それを裏付けるための文献及び説明

VI　☐　ある種の引用文献

VII　☐　国際出願の不備

VIII　☐　国際出願に対する意見

国際予備審査の請求書を受理した日　０７．０４．００	国際予備審査報告を作成した日　２４．０８．００
名称及びあて先 日本国特許庁（ＩＰＥＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	特許庁審査官（権限のある職員）　４Ｐ　９６３８ 榎本　佳予子 電話番号　０３－３５８１－１１０１　内線　３４９２

様式ＰＣＴ／ＩＰＥＡ／４０９（表紙）（１９９８年７月）

国際予備審査報告

国際出願番号　ＰＣＴ／ＪＰ９９／０５１５３

Ⅰ．　国際予備審査報告の基礎

1．　この国際予備審査報告は下記の出願書類に基づいて作成された。（法第６条（ＰＣＴ１４条）の規定に基づく命令に応答するために提出された差し替え用紙は、この報告書において「出願時」とし、本報告書には添付しない。ＰＣＴ規則70.16, 70.17）

[x] 出願時の国際出願書類

[ ] 明細書　第 ＿＿＿＿＿＿＿＿ ページ、　出願時に提出されたもの
明細書　第 ＿＿＿＿＿＿＿＿ ページ、　国際予備審査の請求書と共に提出されたもの
明細書　第 ＿＿＿＿＿＿＿＿ ページ、　＿＿＿＿＿＿＿＿ 付の書簡と共に提出されたもの

[ ] 請求の範囲　第 ＿＿＿＿＿＿＿＿ 項、　出願時に提出されたもの
請求の範囲　第 ＿＿＿＿＿＿＿＿ 項、　ＰＣＴ１９条の規定に基づき補正されたもの
請求の範囲　第 ＿＿＿＿＿＿＿＿ 項、　国際予備審査の請求書と共に提出されたもの
請求の範囲　第 ＿＿＿＿＿＿＿＿ 項、　＿＿＿＿＿＿＿＿ 付の書簡と共に提出されたもの

[ ] 図面　第 ＿＿＿＿＿＿＿＿ ページ／図、　出願時に提出されたもの
図面　第 ＿＿＿＿＿＿＿＿ ページ／図、　国際予備審査の請求書と共に提出されたもの
図面　第 ＿＿＿＿＿＿＿＿ ページ／図、　＿＿＿＿＿＿＿＿ 付の書簡と共に提出されたもの

[ ] 明細書の配列表の部分　第 ＿＿＿＿＿＿＿＿ ページ、　出願時に提出されたもの
明細書の配列表の部分　第 ＿＿＿＿＿＿＿＿ ページ、　国際予備審査の請求書と共に提出されたもの
明細書の配列表の部分　第 ＿＿＿＿＿＿＿＿ ページ、　＿＿＿＿＿＿＿＿ 付の書簡と共に提出されたもの

2．　上記の出願書類の言語は、下記に示す場合を除くほか、この国際出願の言語である。

上記の書類は、下記の言語である ＿＿＿＿＿＿＿＿ 語である。

[ ] 国際調査のために提出されたＰＣＴ規則23.1(b)にいう翻訳文の言語
[ ] ＰＣＴ規則48.3(b)にいう国際公開の言語
[ ] 国際予備審査のために提出されたＰＣＴ規則55.2または55.3にいう翻訳文の言語

3．　この国際出願は、ヌクレオチド又はアミノ酸配列を含んでおり、次の配列表に基づき国際予備審査報告を行った。

[ ] この国際出願に含まれる書面による配列表
[ ] この国際出願と共に提出されたフレキシブルディスクによる配列表
[ ] 出願後に、この国際予備審査（または調査）機関に提出された書面による配列表
[ ] 出願後に、この国際予備審査（または調査）機関に提出されたフレキシブルディスクによる配列表
[ ] 出願後に提出した書面による配列表が出願時における国際出願の開示の範囲を超える事項を含まない旨の陳述書の提出があった
[ ] 書面による配列表に記載した配列とフレキシブルディスクによる配列表に記録した配列が同一である旨の陳述書の提出があった。

4．　補正により、下記の書類が削除された。
[ ] 明細書　第 ＿＿＿＿＿＿＿＿ ページ
[ ] 請求の範囲　第 ＿＿＿＿＿＿＿＿ 項
[ ] 図面　図面の第 ＿＿＿＿＿＿＿＿ ページ／図

5．[ ] この国際予備審査報告は、補充欄に示したように、補正が出願時における開示の範囲を越えてされたものと認められるので、その補正がされなかったものとして作成した。（ＰＣＴ規則70.2(c)　この補正を含む差し替え用紙は上記１．における判断の際に考慮しなければならず、本報告に添付する。）

国際予備審査報告 | 国際出願番号 PCT／JP99／05153

Ⅲ. 新規性、進歩性又は産業上の利用可能性についての国際予備審査報告の不作成

1．次に関して、当該請求の範囲に記載されている発明の新規性、進歩性又は産業上の利用可能性につき、次の理由により審査しない。

☐ 国際出願全体

☒ 請求の範囲 9

理由：

☒ この国際出願又は請求の範囲 9 は、国際予備審査をすることを要しない次の事項を内容としている（具体的に記載すること）。

請求の範囲９は、手術又は治療による人体の処置方法であり、この国際予備審査機関が国際予備審査をすることを要しない対象に係るものである。

☐ 明細書、請求の範囲若しくは図面（次に示す部分）又は請求の範囲 _____ の記載が、不明確であるため、見解を示すことができない（具体的に記載すること）。

☐ 全部の請求の範囲又は請求の範囲 _____ が、明細書による十分な裏付けを欠くため、見解を示すことができない。

☒ 請求の範囲 9 について、国際調査報告が作成されていない。

2．ヌクレオチド又はアミノ酸の配列表が実施細則の附属書Ｃ（塩基配列又はアミノ酸配列を含む明細書等の作成のためのガイドライン）に定める基準を満たしていないので、有効な国際予備審査をすることができない。

☐ 書面による配列表が提出されていない又は所定の基準を満たしていない。

☐ フレキシブルディスクによる配列表が提出されていない又は所定の基準を満たしていない。

Ⅴ．　新規性、進歩性又は産業上の利用可能性についての法第１２条（ＰＣＴ３５条(2)）に定める見解、それを裏付ける文献及び説明

１．　見解

新規性（Ｎ）	請求の範囲	１－８	有
	請求の範囲		無
進歩性（ＩＳ）	請求の範囲		有
	請求の範囲	１－８	無
産業上の利用可能性（ＩＡ）	請求の範囲	１－８	有
	請求の範囲		無

２．　文献及び説明（ＰＣＴ規則70.7）

（文献）
1. ＪＰ，６－１９２１０７，Ａ（株式会社三和化学研究所）（１２．０７．９４）
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4. ＪＰ，５８－５０１１７４，Ａ（ジェー・ビー・ティロット・リミテッド），（２１．０７．８３）
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6. 医薬ジャーナル，Vol.34，S-1，（０１．０１．９８），ｐ．２３７－２４２
7. Drug Delivery，Vol.4，No.3，(1997)，ｐ．２０１－２０６
8. PHARM TECH JAPAN，Vol.11，No.11，(1995)，ｐ．３７－４６
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10. ＪＰ，８－２５３４１３，Ａ（高田寛治），（０１．１０．９６）

（説明）
・請求の範囲１－８について
国際調査報告で引用した上記文献１－３にはグリチルリチンを主薬とする製剤において、グリチルリチンの吸収性を高めるために、大腸等の腸で吸収させる経口投与製剤とすることが記載されている。
そして、当該技術分野において、主薬の吸収性を高めるために大腸で選択的に吸収させることは、引用文献４－１０にも記載されるように周知である。さらに、そのための製剤として、引用文献４には、主薬をアニオン性ポリマーで被覆した経口投与製剤が、上記文献５及び６には、胃溶性皮膜、水溶性皮膜、腸溶性皮膜の順に多層コーティングされたゼラチンカプセルに、主薬が有機酸と共に充填された経口投与製剤が、上記文献７には、開口部がヒドロゲル栓体で閉鎖され、主薬及び担体が充填された水不透性カプセル胴を水溶性カプセルキャップで覆った経口投与製剤が、上記文献８及び９には、大腸溶解性ポリマーで主薬を含有する錠剤を被覆した経口投与製剤が、上記文献１０には、細孔を有する大腸溶解性ポリマー製カプセル内に、ゲル形性材料、主薬及び担体が充填された経口投与製剤がそれぞれ記載されている。
したがって、グリチルリチンを主薬とする製剤としてこれらのいずれかの製剤を適用することは、当業者が容易になし得ることである。
以上のことから、請求の範囲１－８は、新規性は有するが、進歩性を有しない。

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(54) **Colon-specific prodrug, the preparation and uses thereof.**

(57) A colon-specific drug delivery system is based on the use of a synthetic drug glycoside prodrug composition which, when ingested by a mammal, undergoes reaction with glycosidases produced by colonic microflora to release a free drug capable of being absorbed to or absorbed by the intestinal mucosa. Hitherto, synthetic drug glycosides useful in the delivery of chemotherapeutic agents to the colon were not known.

EP 0 123 485 A1

COLON-SPECIFIC PRODRUG, THE PREPARATION AND USES THEREOF

This invention relates to a colon-specific drug delivery system. More specifically, the invention relates to a colon-specific drug delivery system based on the use of a synthetic drug glycoside prodrug composition which, when ingested by a mammal, undergoes reaction with glycosidases produced by colonic microflora to release a free drug capable of being adsorbed to or absorbed by the intestinal mucosa.

In recent years there has been increased emphasis on ways to deliver or activate drugs at specific sites in order to reduce side effects and increase pharmacological response. Implantable pumps, adhesive patches impregnated with drugs, vesicle enclosed drugs, and drug carriers have been proposed to achieve site-specific delivery. Another approach has been to use prodrugs (See Stella, V.J. and Himmelstein, K.J., J. Med. Chem. 23:1275-1282 (1980); Sinkula, A.A. and Yalkosky, S.H., J. Pharm. Sci. 64:181-210 (1975)) which, by virtue of their physicochemical properties, can reach specific sites and then be converted to the active drug in situ. The site-specific delivery of prodrugs administered systemically to the kidney, brain, breasts, or the central nervous system or topically to the eyes or skin have been reported. In all these cases, the parent drug is released chemically or by specific enzyme(s) present at the target site.

It is known that colon-specific delivery of bioactive compounds occurs in man. Anthraquinone cathartics and the carcinogen cyasin are naturally

occurring glycosides found in plants. See Scheline, R.R., J. Pharm. Sci. 57:2021-2137 (1968). Upon ingestion, these substances pass unabsorbed to the large intestine, where the bioactive moieties are released by the enzymatic action of the colonic microflora. The azo-reductase activity of the colonic microflora is now known to activate certain sulfa drugs by reducing the azo-bond present in such compounds. See Mandel, G.L. and Sande, M.A. in "The Pharmacological Basis of Therapeutics", Sixth Ed. (A.G. Gilman, L.S. Goodman, and A. Gilman, Eds.) MacMillan, New York, N.Y., (1980) pp. 1106-1165. Also, the reduction of the azo-link between an unabsorbed polymer and certain aromatic amines form the basis of a recently developed colon-specific drug delivery system. See Parkinson, T.M., Brown, J.P., and Winegard, R.E., U.S. Patent 4,190,716 (Feb. 26, 1980); and Brown, J.P., Appl. Enviro. Microbiol. 41:1283-1286 (1981).

It is also known that the intestinal microflora have unique enzymatic activities capable of hydrolyzing a number of specific chemical bonds. See Drasar, B.S. and Hill, M.J., "Human Intestinal Flora", Academic Press, London, (1974) pp 54-71. However, prior to the present invention it was not known that following ingestion by a mammal, a colon-specific drug glycoside would pass through the stomach and small intestine without being significantly hydrolyzed by endogenous mucosal enzymes produced by the mammalian host. In addition, prior to the present invention it was not known that such a drug glycoside prodrug would pass into the area of the colon where it would be essentially cleaved by the glycosidase activity of colonic microflora. Prior to the teaching of the present invention, it was also not known that once such cleavage of the prodrug occurred, a free drug capable

of being adsorbed to or absorbed by the intestinal mucosa would be released.

Such a synthetic prodrug comprised of a drug glycoside has advantages over the compounds used in the colon-specific delivery systems of the prior art. The fact that the prodrug is synthetic makes it possible to create drug glycosides not found in nature. For example, synthetic drug glycosides are disclosed herein that are useful in the treatment of ulcerative colitis, a condition which carries an increased risk of colon cancer, and other forms of inflammatory bowel disease. Natural drug glycosides useful for the treatment of inflammatory bowel disease are not found in nature. Synthetic drug glycosides of the type disclosed herein will also be useful in the delivery of chemotherapeutic agents to the colon and then to liver metastases with minimal damage to the stomach and small intestine. Synthetic drug glycosides useful in the delivery of chemotherapeutic agents to the colon are not found in nature.

The drug glycosides of the present invention utilize simple sugars as the disabling moiety that substantially prevents liberation or absorption of the free drug until the prodrug reaches the area of the colon. Colonic microfloral glycosidases then act upon the drug glycoside, liberating the sugar moiety from the drug moiety. These liberated sugar residues can be utilized as an energy source by the intestinal bacteria. Although the nonabsorbable polymeric backbone utilized in the colon-specific drug delivery system disclosed in U.S. Patent 4,190,716 may prove harmless to patients exposed to the polymers for considerable lengths of time, the long term effect of these compounds has not yet been evaluated. On the other hand, the colon-specific drug delivery system

disclosed herein leaves no such unnatural waste compound for the body to contend with.

It is an aspect of the invention to provide a colon-specific drug delivery system useful for the treatment of disease that will utilize a synthetic prodrug comprised of a drug glycoside capable of being essentially cleaved by glycosidase enzymatic activity of colonic microflora but not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host, thus enabling the most significant amounts of free drug to be released in the area of the colon following cleavage of the drug glycoside by glycosidases produced by the colonic microflora.

It is a further aspect of the invention to provide a colon-specific drug delivery system useful for the treatment of disease that will utilize a synthetic prodrug comprised of a steroid glycoside capable of being essentially cleaved by glycosidase enzymatic activity of colonic microflora but not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host, thus enabling the most significant amounts of free drug to be released in the area of the colon following cleavage of the drug glycoside by glycosidases produced by the colonic microflora.

It is a further aspect of the invention to provide a colon-specific synthetic prodrug composition comprised of a steroid glycoside capable of being essentially cleaved by beta-galactosidase enzymatic activity of colonic microflora but not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host, thus enabling the most significant amounts of free drug to be released in the area of the colon following cleavage of the drug

glycoside by glycosidases produced by the colonic microflora.

It is a further aspect of the invention to provide a colon-specific synthetic prodrug composition comprised of a steroid glycoside capable of being essentially cleaved by alpha-galactosidase enzymatic activity of colonic microflora but not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host thus enabling the most significant amounts of free drug to be released in the area of the colon following cleavage of the drug glycoside by glycosidases produced by the colonic microflora.

It is a further aspect of the invention to provide a method for producing a colon-specific synthetic prodrug composition comprised of a steroid glycoside capable of being essentially cleaved by beta-glucosidase enzymatic activity of colonic microflora but not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host thus enabling the most significant amounts of free drug to be released in the area of the colon following cleavage of the drug glycoside by glycosidases produced by the colonic microflora.

It is a further aspect of the invention to provide a method for producing a colon-specific synthetic prodrug composition comprised of a steroid drug glycoside capable of being essentially cleaved by beta-cellobiosidase enzymatic activity of colonic microflora but not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host thus enabling the most significant amounts of free drug to be released in the area of the colon following cleavage of the drug glycoside by glycosidases produced by the colonic microflora.

Other objects of the invention will become apparent to those skilled in the art from the following description, taken in connection with the accompanying drawings.

FIGURE 1 is a chemical formula chart illustrating preparation and enzymatic hydrolysis of glucosides 1 and 2;

FIGURE 2 is a drawing showing a HPLC chromatogram of the cecal contents of a rat given of glucoside 1 and sacrificed six hours later;

FIGURE 3 is a drawing of graphs illustrating recovery of steroid glycoside and free steroid at various times after intragastric administration of the glycosides 1 and 2;

FIGURE 4 is a drawing of graphs illustrating recovery of steroid at various times after intragastric administration of the free steroids prednisolone and dexamethasone;

FIGURE 5 is a drawing of graphs illustrating the hydrolysis of p-nitrophenyl-glucoside at several concentrations, plotted by the Eadie-Hoffstee method to determine Vmax and Km(app).

FIGURE 6 is a drawing of graphs illustrating the hydrolysis of p-nitrophenyl-galactoside at several concentrations, plotted by the Eadie-Hoffstee method to determine Vmax and Km(app).

In the chart of FIGURE 1, "a" is Ag_2CO_3, molecular sieve, CCl_4; "b" is 0.01 N NaOH, MeOH; and "c" is beta-glucosidase; 1, 2, 3, 4, 23, 14 and 15 are compounds 1, 2, 3, 4, 23, 14 and 15 respectively; the letter R means radical and the letters Ac mean acetyl. The other letters, g., O, H, F and Br denote the chemical elements oxygen, hydrogen, fluorine and bromine, respectively.

In the chromatogram of FIGURE 2, Peak A is glucoside 1; Peak B is dexamethasone, 3; and Peak C is prednisolone, 4, added as an internal standard prior to homogenization. To obtain the chromatogram, an Altex 5 micrometer Ultrasphere, C-18 column was eluted with MeOH/0.01 M KH_2PO_4 (56.5:43.5) at a flow rate of 1.2 mL/min.

The graphs of FIGURE 3 illustrate recovery of steroid glycoside and free steroid at various times after intragastric administration of 7.5 mg of glucoside 1 (panels A and B) and glucoside 2 (panels C and D). Data are given as means ±SEM (n=4). Solid circle and triangle symbols indicate intestinal contents; and open circle and triangle symbols indicate intestinal tissues.

The graphs of FIGURE 4 illustrate recovery of steroid at various times after intragastric administration of the free steroids dexamethasone, 3, (5.10 mg) and prednisoone, 4, (5.25 mg). Data points are means ±SEM (n=3) from intestinal contents, shown as solid circles, and tissues, shown as open circles.

The graph of FIGURE 5 illustrates the velocity-substrate relationship for hydrolysis of p-nitrophenyl-glucoside by cecal contents at lower substrate concentrations. Hydrolysis was followed by measuring the release of p-nitrophenol spectrophotometrically at 403 nm. Eadie-Hofstee plots were used to determine the $K_{M(app)}$ and V_{max}. The Eadie-Hofstee plot of the relationship deviated from linearity suggesting that beta-D-glucosidase activity may be more heterogenous in nature than beta-D-galactosidase activity.

The graph of FIGURE 6 illustrates the velocity-substrate relationship for hydrolysis of p-nitrophenyl-galactoside by cecal contents. Again,

hydrolysis was followed by measuring the release of p-nitrophenol spectrophotometrically at 403 nm. Eadie-Hofstee plots were used to determine the $K_{M(app)}$ and V_{max}. The Eadie-Hofstee plot is linear.

In the present description and claims reference will be made to several terms which are expressly defined for use herein as follows.

Colonic microflora - gastrointestinal bacteria found essentially exclusively in the colonic area of the mammalian gastrointestinal tract.

Colon-specific - essentially exclusive to the colonic area of the mammalian gastrointestinal tract.

PSI - proximal small intestine.

DSI - distal small intestine.

Endogenous enzymes - enzymes produced by the mammalian host (as opposed to enzymes produced by bacteria found within the mammalian intestine) that are secreted into the mammalian gastrointestinal tract.

Natural - produced in nature. As used herein, natural will refer to compounds produced in living organisms.

Synthetic - produced by synthesis. As used herein, synthetic will refer to compounds not produced in nature.

Simple sugar - a monosaccharide, a disaccharide or an oligosaccharide.

Aglycone - a compound having no sugar attached thereto by means of a glycosidic bond.

Glycoside - a compound which contains a sugar moiety and an aglycone moiety attached to one another by means of a glycosidic linkage.

Glycosidic link - a link between an aglycone and the reducing end of a sugar.

Drug - any chemical compound or any

noninfectious biological substance, not used for its mechanical properties, which may be administered to or used on or for patients, either human or animal, as an aid in the diagnosis, treatment or prevention of disease or other abnormal condition, for the relief of pain or suffering, or to control or improve any physiological or pathological condition.

Prodrug - a latent form of an active drug with certain physicochemical properties that allow it to reach a target organ or tissue. Once there, the active drug is formed chemically or enzymatically in situ.

Hydrophilicity - the state of being hydrophilic.

Most significantly - the most measurable amount. As used herein, the prase denotes the relative amount of aglycone released following cleavage of the glycosidic link on the prodrug when release occurs in the area of the colon as compared with release in other areas of the mammalian gastrointestinal tract.

Scientific publications and patents cited herein are expressly incorporated by reference.

The following compounds are referred to in the present description and claims:

Compound 1 is 9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-16 alpha-methyl-3, 20-dioxopregna-1, 4-dien-21-yl beta-D-glucopyranoside; it is referred to herein as "compound 1", "(1)", "1", DEXAGLU, or dexamethasone-glucoside.

Compound 2 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-1, 4-dien-21-yl beta-D-glucopyranoside; it is referred to herein as "compound 2", "(2)", "2", PREDGLU, or prednisolone-glucoside.

Compound 3 is 9 alpha-Fluoro-11 beta, 17 alpha-21 trihydroxy-16 alpha-methyl-3, 20-dioxopregna-

1, 4-diene; it is referred to herein as "compound 3", "(3)", "3", "dexa", or dexamethasone.

Compound 4 is 11 beta, 17 alpha-21-Trihydroxy-3, 20-dioxpregna-1, 4-diene; it is referred to herein as "compound 4", "(4)", "4", "pred", or prednisolone.

Compound 5 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-4-en-21-yl beta-D-glucopyranoside; it is referred to herein as "compound 5", "(5)", "5", or hydrocortisone-glucoside.

Compound 6 is 11 beta, 17 alpha-21-Trihydroxy-3, 20-dioxopregna-4-ene; it is referred to herein as "compound 6", "(6)", "6", or hydrocortisone.

Compound 7 is 9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-3, 20-dioxopregna-4-en-21-yl beta-D-glucopyranoside; it is referred to herein as "compound 7", "(7)", "7", or fludrocortisone-glucoside.

Compound 8 is 9 alpha-Fluoro-11 beta, 17 alpha-21-trihydroxy-3, 20-dioxopregna-4-ene; it is referred to herein as "compound 8", "(8)", "8", or fludrocortisone.

Compound 9 is 9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-16 alpha-methyl-3, 20-dioxopregna-1, 4-dien-21-yl beta-D-galactopyranoside; it is referred to herein as "compound 9", "(9)", "9", or dexamethasone-galactoside.

Compound 10 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-4-en-21-yl beta-D-galactopyranoside; it is referred to herein as "compound 10", "(10)", "10", or prednisolone-galactoside.

Compound 11 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-4-en-21-yl beta-D-galactopyranoside; it is referred to herein as "compound 11", "(11)", "11", or hydrocortisone-galactoside.

Compound 12 is 9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-3, 20-dioxopregna-4-en-21-yl beta-

D-galactopyranoside; it is referred to herein as "compound 12", "(12)", "12", or fludrocortisone-galactoside.

Compound 13 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-1, 4-diene-21-yl beta-D-cellbioside; it is referred to herein as "compound 13", "(13)", "13", or prednisolone-cellobioside.

Compound 14 is 9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-16 alpha-methyl-3, 20 dioxo pregna-1, 4-dien-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-glucopyranoside; it is referred to herein as "compound 14", "(14)", "14", or DEXATAGLU.

Compound 15 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-1, 4-dien-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-glucoside; it is referred to herein as "compound 15", "(15)", "15", or PREDTAGLU.

Compound 16 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-4-en-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-glucopyranoside; it is referred to herein as "compound 16", "(16)", "16", or hydrocortisone tetraacetyl glucoside.

Compound 17 is 9 alpha-Fluoro-11 beta, 17 alpha dihydroxy-3, 20-dioxopregna-4-en-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-glucopyranoside; it is referred to herein as "compound 17", "(17)", "17", or fludrocortisone tetraacetyl glucoside.

Compound 18 is 9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-16 alpha-methyl-3, 20-dioxopregna-1, 4-dien-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-galactopyranoside; it is referred to herein as "compound 18", "(18)", "18", or dexamethasone tetraacetyl galactoside.

Compound 19 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-1, 4-dien-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-galactopyranoside; it is referred t here

as "compound 19", "(19)", "19", or prednisolone tetraacetyl galactoside.

Compound 20 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-4-en-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-galactopyranoside; it is referred to herein as "compound 20", "(20)", "20", or hydrocortisone tetraacetyl galactoside.

Compound 21 is 9 alpha-Fluoro-11 beta, 17 alpha dihydroxy-3, 20-dioxopregna-4-en-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-galactopyranoside; it is referred to herein as "compound 21", "(21)", "21", or fludrocortisone tetraacetyl galactoside.

Compound 22 is 11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-1, 4-dien-21-yl hepta-O-acetyl-beta-D-cellobioside; it is referred to herein as "compound 22", "(22)", "22", or prednisolone heptaacetyl cellobioside.

Compound 23 is 2, 3, 4, 6-tetra-O-acetyl-1-bromo-alpha-D-glucopyranose; it is referred to herein as "compound 23", "(23)", "23", or tetraacetyl-1-bromo-glucose.

Compound 24 is 2,3,4,6-tetra-O-acetyl-1-bromo-alpha-D-galactopyranose; it is referred to herein as "compound 24", "(24)", "24", or tetraacetyl-1-bromo-galactose.

Compound 25 is hepta-O-acetyl-1-bromo-alpha-D-cellobiose; it is referred to herein as "compound 25", "(25)", "25", or heptaacetyl-1-bromo-alpha-cellobiose.

All steroids, 2,3,4,6-tetra-O-acetyl-1-bromo-alpha-D-glucopyranose, 2,3,4,6-tetra-O-acetyl-1-bromo-alpha-D-galactopyranose, p-nitrophenyl substrates, and p-nitrophenol were purchased from Sigma Chemical Co. Octa-O-acetyl-alpha-D-cellobiose was obtained from Aldrich Chemical Co. and the 31% hydrobromic acid in

acetic acid was purchased from Eastman Kodak Co.

Preparative methods and assays utilized in the disclosure of the present invention include:

PREPARATIVE METHODS

SOLVENTS

All solvents were redistilled and dried over molecular sieves, 4 angstrom, 4-8 mesh (Aldrich Chemical Co.). All solvent evaporations were performed with a rotary evaporator with water aspirator reduced pressure. Melting points were obtained on a Buchi melting point apparatus and are uncorrected. UV spectra were determined on a Cary 210 spectrometer. IR spectra were determined on a Perkin Elmer Model 137 spectrometer. ^1H NMR spectra were determined on either the UCB 200 or the UCB 250 (home-made 200 and 250-MHz Fourier transform devices located in the College of Chemistry, University of California, Berkeley) and were recorded in dimethyl-d_6 sulfoxide; they are expressed in parts per million (delta) downfield from Me_4Si with coupling constants (J) expressed in hertz. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley. Analyses were within ± 0.4% of theoretical values except where noted.

CHROMATOGRAPHY

High-pressure liquid chromatography (HPLC) was performed on an Altex analytical system consisting of two model 110A pumps, a model 160 UV detector, a model 420 microprocessor/programmer and a stainless steel column (4.6 x 25 cm, 5 micrometer Ultrasphere C-18). A flow rate of 1.2 mL/min was used, with absorbance monitoring at 254 nm. The solvent system for all separations was MeOH/0.01 M KH_2PO_4 (56.5:43.5). Low-pressure preparative chromatography (flash chromatography, J.T. Baker Chem. Co.) was performed

using either a 3.7 x 22 cm column of 40 micrometer RP-18 with MeOH/water (68:32) as eluent or a 3.0 x 18 cm column of 40 micrometer silica gel with $CHCl_3$/95% EtOH (65:35) as eluent. TLC was performed on aluminum-backed plates of silica gel 60 (E. Merck Co.). Steroids and their glycosides were identified by spraying the developed plates with toluenesulfonic acid/95% EtOH (20:80, w/v) and heating for 10 min at 110°C.

SYNTHESIS

COMPOUND 15: PREDTAGLU

11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-1, 4-dien-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-glucoside.

PREDNISOLONE 4, (1.20 g, 3.33 mmoles) was dissolved in dry $CHCl_3$ (30 ml) and added to dry, boiling $CHCl_3$ (200 ml) over 4 angstrom molecular sieves in a 500 ml round bottom flask. After 10-20 ml had been distilled, freshly prepared (See McCloskey, C.M. and Colman, G.H., in "Organic Synthesis" Coll. Vol. 3, Wiley, New York, N.Y. (1955) pp 434-435) silver carbonate (3.90 g, 14.1 mmoles) was added to the flask. Then a solution of 2,3,4,6-tetra-O-acetyl-1-bromo-alpha-D-glucopyranose (23, 3.50 g, 8.50 mmoles) in dry $CHCl_3$ (100 ml) was added dropwise from an addition funnel. The reaction mixture was protected from light and stirred throughout. The addition of bromosugar took approximately 1 hr., and the solvent was distilled continuously during this time. Distillation was continued for an additional hour after all the bromosugar had been added; volume was maintained by the addition of dry $CHCl_3$. The solution was filtered, washed with cold, saturated NaCl, dried with sodium sulfate, and the solvent removed. The oily residue was dissolved in several milliliters of methanol and

purified by flash chromatography on RP-18. The appropriate fractions were collected and the solvent removed. Crystallization of PREDTAGLU from methanol/water yielded 0.87 g (38%); MP: 119-121°C; TLC: R_f 0.36 (ethyl acetate/isooctane 9:1); UV lambda(max): 242 nm (epsilon 13500); IR(KBr): 3450 (OH), 1760 (acetyl), 1650 (C=O), 1190 (acetyl), 896 cm^{-1}; ^1H-NMR: delta 0.77 (s, 3H, C-18), 1.45 (s, 3H, C-19), 1.99 (s, 9H, C-2',3',4' acetyl), 2.08 (s, 3H, C-6' acetyl), 4.20 (d, 1H, C-1', J=8), 4.58 (AB, q, 2H, C-21, J=18, 5.92 (s, 1H, C-4), 6.15 (d, 1H, C-2, J=11), 7.40 (d, 1H, C-1, J=11). Anal. ($C_{35}H_{46}O_{14}$) C, H.

COMPOUND 14: DEXATAGLU

9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-16 alpha-methyl-3, 20 dioxopregna-1, 4-dien-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-glucopyranoside.

DEXATAGLU, 14, was prepared from dexamethasone, 3, as described for PREDTAGLU, 15, from prednisolone, 4. Crystallization of DEXATAGLU from methanol/water yielded 0.55 gm (25%); MP: 119.5-121°C; TLC: R_f 0.45 (ethyl acetate/isooctane, 9:1); UV lambda(max): 239 nm (epsilon 14300), IR(KBr): 3450 (OH), 1760 (acetyl), 1650 (C=O), 1190 (acetyl), 896 cm^{-1}; ^1H NMR: delta 0.76 (d, 3H, C-16 alpha CH_3, J=6), 0.88 (s, 3H, C-18), 1.49 (s, 3H, C-19), 2.00 (s, 9H, C-2', 3', 4', acetyl), 2.09 (s, 3H, C-6' acetyl), 4.18 (d, 1H, C-1', J=8), 4.57 (AB q, 2H, C-21, J=18), 6.02 (s, 1H, C-4), 6.23 (d, 1H, C-1, J=11), 7.33 (d, 1H, C-2 J=11). Anal. Calc. for $C_{36}H_{47}O_{14}F$: C, 59.75; H, 6.63. Found: C, 59.08 H, 6.54.

COMPOUND 2: PREDNISOLONE-GLUCOSIDE

11 beta, 17 alpha-Dihydroxy-3, 20-dioxopregna-1, 4-dien-21-yl beta-D-glucopyranoside.

PREDTAGLU, 15, (0.20 g, 0.38 mmoles) was

dissolved in methanol (10 ml) and benzene (5.0 ml). 0.04 N NaOH in methanol (5.0 ml) was then added. The reaction was run under N_2 at room temperature with stirring. After thirty min., several drops of acetic acid were added to neutralize the solution. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel. The appropriate fractions were combined, the solvent removed under reduced pressure, and the residue dissolved in a tert-butyl alcohol/water (15 ml., 1:1) solution. This solution was frozen and the solvent removed by lyophilization. Yield was 0.11 g (73%); TLC: R_f 0.58 (chloroform/95% ethanol, 3:2); UV lambda(max): 242 nm (epsilon 13200); IR(KBr): 3450 (-OH), 1650 (C=O), 896 cm^{-1}; ^1H-NMR: delta 0.77 (s, 3H, C-18), 1.45 (s, 3H, C-19), 4.20 (d, 1H, C-1', J=8), 4.58 (AB q, 2H, C-21, J=18), 5.92 (s, 1H, C-4), 6.15 (d, 1H, C-1, J=11), 7.40 (d, 1H, C-2, J=11). Anal. Calc. for $C_{27}H_{38}O_{10}\cdot H_2O$: C, 60.00; H, 7.41. Found: C, 59.94; H, 7.64.

COMPOUND 1: DEXAMETHASONE-GLUCOSIDE

9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-16 alpha-methyl-3, 20-dioxopregna-1, 4-dien-21-yl beta-D-glucopyranoside.

Compound 1 was prepared from DEXATAGLU, 14, as described for prednisolone glucoside, 2, from PREDTAGLU, 15. Yield was 0.12 gm (75%); TLC: R_f 0.51 (chloroform/95% ethanol, 3:2); UV lambda(max): 239 nm (epsilon 14500); IR(KBr): 3450 (-OH), 1650 (C=O), 896 cm^{-1}; ^1H NMR: delta 0.78 (d, 3H, C-16 alpha methyl, J=7), 0.88 (s, 3H, C-18), 1.49 (s, 3H, C-19), 4.17 (d, 1H, C-1'; J=8), 4.57 (AB q, 2H, C-21, J=18), 6.03 (s, 1H, C-4), 6.23 (d, 1H, C-1, J=11), 7.35 (d, 1H, C-2, J=11). Anal. Calc. for $C_{28}H_{39}O_{12}F\cdot H_2O$: C, 58.43; H, 7.65. Found: C, 58.58; H, 7.36.

COMPOUND 18: DEXAMETHASONE TETRAACETYL GALACTOSIDE

9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-16 alpha-methyl-3,20-dioxopregna-1,4-dien-21-yl 2',3',4',6'-tetra-O-acetyl-beta-D-galactopyranoside.

Compound 18 was prepared from dexamethasone, 3, as described for PREDTAGLU, 15, from steroid 4, prednisolone. Crystallization of 18 from MeOH/water yielded 0.56 g (26%); MP: 133-135°C; TLC: R_f 0.39 (ethyl acetate/isooctane, 9:1); UV lambda(max): 239 nm (epsilon 15400); IR(KBr): 3450 (OH), 1750 (OAc), 1660 (C=O), 1620 (C=C), 1240 (OAc), 985, 960, 895 cm^{-1}; ^1H NMR delta 0.78 (d, 3H, C-16 CH_3), 0.88 (s, 3H, C-18), 1.49 (s, 3H, C-19), 1.93 (s, 3H, C-4' OAc), 2.00 (s, 3H, C-3' OAc), 2.06 (s, 3H, C-2' OAc), 2.12 (s, 3H, C-6' OAc), 4.18 (d, 1H, C-1', J=7.2), 4.52 (ABq, 2H,C-21, J=18.3), 6.01 (s, 1H, C-2, J=11), 7.32 (d, 1H, C-1, J=10). Anal. ($C_{36}H_{47}O_{14}F$) C, H.

COMPOUND 19: PREDNISOLONE TETRAACETYL GALACTOSIDE

11 beta, 17 alpha-Dihydroxy-3,20-dioxopregna-1,4-dien-21-yl 2',3',4',6'-tetra-O-acetyl-beta-D-galactopyranoside.

Compound 19 was prepared from prednisolone (4) as described for PREDTAGLU, 15, from steroid 4, prednisolone. Crystallization of 19 from MeOH/water yielded 0.82 g (37%); MP: 134-136°C; TLC: R_f 0.39 (ethyl acetate/isooctane, 9:1; UV lambda(max): 242 nm (epsilon 14700); IR(KBr): 3500 (OH), 1760 (OAc), 1650 (C=O), 1620 (C=C), 1240 (OAc), 900 cm^{-1}; ^1H NMR delta 0.78 (s, 3H, C-18), 1.38 (s, 3H, C-19), 1.91 (s, 3H, C-4' OAc), 1.99 (s, 3H, C-3' OAc), 2.03 (s, 3H, C-2' OAc), 2.09 (s, 3H, C-6' OAc), 4.23 (d, 1H, C-1', J=7.2), 4.49 (ABq, 2H, C-21, J=18), 5.92 (s, 1H, C-4), 6.15 (d, 1H, C-1, J=11), 7.40 (d, 1H, C-2, J=11). Anal. ($C_{35}H_{46}O_{14}$) Calcd: C, 60.78; H, 6.66. Found: C, 59.83; H, 6.89.

COMPOUND 16: HYDROCORTISONE TETRAACETYL GLUCOSIDE

11 beta, 17 alpha-Dihydroxy-3,20-dioxopregna-4-en-21-yl 2',3',4',6'-tetra-O-acetyl-beta-D-glucopyranoside.

Compound 16 was prepared from hydrocortisone (6) and bromo sugar 23 as described for glucoside 15 from steroid 4 and bromo sugar 23. Crystallization of 16 from MeOH/water yielded 0.52 g (23%); MP: 120.5-122°C; TLC: R_f 0.39 (ethyl acetate/isooctane, 9:1); UV lambda(max): 242 nm (epsilon 15700); IR(KBr): 3450 (OH), 1760 (OAc), 1645 (C=O), 1610 (C=C), 1240 (OAc), 950, 908, 875 cm^{-1}; ^1H NMR delta 0.80 (s, 3H, C-18, 1.40 (s, 3H, C-19), 1.96 (s, 3H C-4' OAc), 1.99 (s, 3H, C-3' OAc), 2.04 (s, 3H, C-2' OAc), 2.05 (s, 3H, C-6' OAc), 4.20 (d, 1H, C-1', J=7.5), 4.60 (ABq, 2H, C-21, J=18), 5.60 (s, 1H, C-4. Anal. ($C_{35}H_{48}O_{14}$) H; C: calcd, 60.69; found 60.02.

COMPOUND 20: HYDROCORTISONE TETRAACETYL GALACTOSIDE

11 beta, 17 alpha-Dihydroxy-3,20-dioxopregna-4-en-21-yl 2',3',4',6'-tetra-O-acetyl-beta-D-galactopyranoside.

Compound 20 was prepared from steroid 6 and bromo sugar 24 as described for glucoside 15 from steroid 4. Crystallization of 20 from MeOH/water yielded 0.57 g (26%); MP: 122-124°C; TLC: R_f 0.42 (ethyl acetate/isooctane); UV lambda(max): 242 nm (epsilon 16700); IR(KBr): 3450 (OH), 1760 (OAc), 1660 (C=O), 1620 (C=C), 1230 (OAc), 950, 908, 896 cm^{-1}; ^1H NMR delta 0.80 (s, 3H, C-18), 1.42 (s, 3H, C-19, 1.92 (s, 3H, C-4' OAc), 1.98 (s, 3H, C-3' OAc), 2.04 (s, 3H, C-2' OAc), 2.09 (s, 3H, C-6' OAc), 4.24 (d, 1H, C-1', J=7.6), 4.58 (ABq, 2H;, C-21, J=18), 5.60 (s, 1H, C-4). Anal. ($C_{35}H_{48}O_{14}$) H, C: calcd, 60.69; found, 60.27.

COMPOUND 17: FLUDROCORTISONE TETRAACETYL GLUCOSIDE

9 alpha-Fluoro-11 beta, 17 alpha-dihdroxy-3,

20-dioxopregna-4-en-21-yl 2',3',4',6'-tetra-O-acetyl-beta-D-glucopyranoside.

Compound 17 was prepared from fludrocortisone 8 as described for glucoside 15 from steroid 4. Crystallization of 17 from MeOH/water yielded 0.48 g (23%); MP: 124-125°C; TLC: R_f 0.39 (ethyl acetate/isooctane); UV lambda(max): 239 nm (epsilon 17500); IR(KBr): 3450 (OH), 1750 (OAc), 1660 (C=O), 1625 (C=C), 1250 (OAc), 898 cm^{-1}; ^1H NMR delta 0.76 (s, 3H, C-18), 1.49 (s, 3H, C-19), 1.95 (s, 3H, C-4' OAc), 2.00 (s, 6H, C-2',3' OAc), 2.04 (s, 3H, C-6' OAc), 4.25 (d, 1H, C-1', J-7.8), 4.45 (ABq, 2H, C-21, J=18, 5.75 (s, 1H, C-4). Anal. ($C_{35}H_{47}O_{14}F$) C, H.

COMPOUND 21: FLUDROCORTISONE TETRAACETYL GALACTOSIDE

9 alpha-Fluoro-11 beta, 17 alpha dihydroxy-3, 20-dioxopregna-4-en-21-yl 2', 3', 4', 6'-tetra-O-acetyl-beta-D-galactopyranoside.

Compound 21 was prepared from steroid 8 and bromo sugar 24 as described for glucoside 15 from steroid 4 and bromo sugar 23. Crystallization of 21 from MeOH/water yielded 0.45 g (23%); MP: 130-132°C; TLC: R_f 0.40 (ethyl acetate/isooctane); UV lambda(max): 239 nm (epsilon 17100); IR(KBr): 3500 (OH), 1780 (OAc), 1660 (C=O), 1620 (C=C), 1250 (OAc) cm^{-1}; ^1H NMR: delta 0.78 (s, 3H, C-18), 1.48 (s, 3H, C-19), 1.92 (s, 3H, C-4' OAc), 1.99 (s, 3H, C-3' OAc), 2.03 (s, 3H, C-2' OAc), 2.09 (s, 3H, C-6' OAc), 4.25 (d, 1H, C-1', J=8), 4.53 (ABq, 2H, C-21, J=18), 5.73 (s, 1H, C-4). Anal. ($C_{35}H_{47}O_{14}F$) C, H.

COMPOUND 25:- HEPTAACETYL-1-BROMO-ALPHA CELLOBIOSE

Hepta-O-acetyl-1-bromo-alpha-D-cellobiose, was prepared according to published procedures. See Bollenback, G.N., Long, J.W., Benjamin, D.G., Lindquist, J.A., J. Am. Chem. Soc., 77:3310 (1955); Freudenberg, K., Nagai, W., Ann., 494:63 (1932).

Octa-O-acetyl-alpha-D-cellobiose (7.5 g, 11.1 mmol) was dissolved in 31% HBr in acetic acid (35 mL). The mixture was stirred at 4 degrees C for 24 h. Then icecold water (5 mL) was added, followed by $CHCl_3$ (10 mL). The organic phase was then washed several times with cold saturated NaCl solution, and dried (Na_2SO_4). Bromo sugar 25 was crystallized by addition of dry ethyl ether to yield 4.68 g (61%); MP: 181-182°C (lit. MP 183°C, (See Freudenberg and Nagai, supra), $[\alpha]_D^{27}$ +93.5 (c 5.4 $CHCl_3$), (lit. $[\alpha]_D^{20}$ +95.8. See Haynes, L.J., Newth, F.H., Adv. Carbohydr. Chem., 10:213 (1955).

COMPOUND 22: PREDNISOLONE HEPTAACETYL CELLOBIOSIDE

11 beta, 17 alpha-Dihydroxy-3,20-dioxopregna-1,4-dien-21-yl Hepta-O-acetyl-beta-D-cellobioside.

Compound 22 was prepared from steroid 4 (0.6 g, 1.6 mmol) and bromo sugar 25 (3.7 g, 5.2 mmol) as described for the preparation of glucoside 15 from steroid 4 and bromo sugar 23. Crystallization of 22 from MeOH/water yielded 0.42 g (25%); MP: 135-136°C; TLC: R_f 0.39 (ethyl acetate/isooctane); UV lambda(max): 242 nm (epsilon 16900); IR(KBr): 3500 (OH), 1750 (OAc), 1660 (C=O), 1620 (C=C), 1230 (OAc), 912, 870, 782 cm^{-1}; ^1H NMR delta 0.78 (s, 3H, C-18), 1.42 (s, 3H, C-19), 1.91 (s, 3H, OAc), 1.97 (s, 6H, OAc), 1.99 (s, 3H, OAc), 2.01 (s, 6H, OAc), 2.07 (s, 3H, OAc), 4.28 (d, 1H, C-1', J=7.6), 4.49 (ABq, 2H, C-21, J=18), 5.92 (s, 1H, C-4), 6.15 (d, 1H, C-2, J=11), 7.40 (d, 1H, C-1, J=10. Anal. ($C_{47}H_{62}O_{22}$) C, H.

COMPOUND 5: HYDROCORTISONE-GLUCOSIDE

11 beta, 17 alpha-Dihydroxy-3,20-dioxopregna-4-en-21-yl beta-D-glucopyranoside.

To prepare glucoside 5, acetyl glucoside 16 (0.2 g, 0.32 mmol) was dissolved in MeOH (10 mL) and benzene (5 mL). NaOH in MeOH (0.04 N, 5.0 mL) was th n

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added. The reaction was run under N_2 at room temperature with stirring. After 45 min, several drops of acetic acid were added to neutralize the solution. The solvent was removed and the residue was purified by flash chromatography on silica gel. Purified glucoside 16 was then dissolved in tert-butyl alcohol/water (15 mL, 1:1). This solution was frozen, and the solvent was removed by lyophilization to yield 0.12 mg (77%); R_f 0.49 ($CHCl_3$/95% EtOH, 65:35); UV lambda(max): 242 nm (epsilon 15800); IR(KBr): 3450 (OH), 1650 (C=O), 1620 (C=C), 945, 910, 868 cm^{-1}; ^1H NMR delta 0.76 (s, 3H, C-18), 1.36 (s, 3H, C-19), 4.17 (d, 1H, C-1', J=7.7), 4.57 (ABq, 2H, C-21, J=18.2), 5.56 (s, 1H, C-4). Anal. ($C_{27}H_{40}O_{10}H_2O$) C, H.

COMPOUND 7: FLUDROCORTISONE-GLUCOSIDE

9 alpha-Fluoro-11 beta,17 alpha-dihydroxy-3, 20-dioxopregna-4-en-21-yl beta-D-glucopyranoside.

Compound 7 was prepared from acetyl glucoside 17 as described for glucoside 5 from acetyl glycoside 16. After lyophilization, 0.11 g (71%) of glucoside 7 was obtained; TLC: R_f 0.50 ($CHCl_3$/95% EtOH, 7:3); UV lambda(max): 239 nm (epsilon 17800); IR(KBr): 3450 (OH), 1650 (C=O), 1620 (C=C), 938, 895 cm^{-1}; ^1H NMR delta 0.78 (s, 3H, C-18), 1.49 (s, 3H, C-19), 4.19 (d, 1H, C-1', J=7.6, 4.57 (ABq, 2H, C-21, J=18), 5.70 (s, 1H, C-4). Anal. ($C_{27}H_{40}O_{10}F\cdot H_2O$) H. C: Calcd, 57.96; found, 58.53.

COMPOUND 9: DEXAMETHASONE-GALACTOSIDE

9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-16 alpha-methyl-3,20-dioxopregna-1,4-dien-21-yl beta-D-galactopyranoside.

Compound 9 was prepared from acetyl galactoside 18 as described for glucoside 5 from acetyl glucoside 16. After lyophilization, 95 mg (60%) of galactoside 9 was obtained; TLC: R_f 0.46

($CHCl_3$/95% EtOH, 7:3); UV lambda(max): 239 nm (epsilon 14400); IR(KBr): 3450 (OH), 1680 (C=O), 1625 (C=C), 990, 891 cm^{-1}; ^1H NMR delta 0.76 (d, 3H, C-16 $-CH_3$, J=7), 0.85 (s, 3H, C-18), 1.50 (s, 3H, C-19), 4.19 (d, 1H, C-1', J=7.8), 4.58 (ABq, 2h, C-21, J=18), 6.01 (s, 1H, C-4), 6.24 (d, 1H, C-1, J=10.1), 7.39 (d, 1H, C-2, J=10.2). Anal. ($C_{28}H_{39}O_{10}F \cdot H_2O$) calcd: C, 60.65; H, 7.17. Found: C, 60.44; H, 6.98.

COMPOUND 10: PREDNISOLONE-GALACTOSIDE

11 beta, 17 alpha-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl beta-D-galactopyranoside.

Compound 10 was prepared from acetyl galactoside 19 as described for glucoside 5 from acetyl glucoside 16. After lyophilization, 0.13 g (83%) of galactoside 10 was obtained; TLC: R_f 0.39 ($CHCl_3$/95% EtOH, 7:3); UV lambda(max): 242 nm (epsilon 14500); IR(KBr): 3450 (OH), 1650 (C=O). 1615 (C=C), 899 cm^{-1}; ^1H NMR delta 0.78 (s, 3H, C-18), 1.39 (s, 3H, C-19), 4.13 (d, 1H, C-1', J=7.3), 4.53 (ABq, 2H, C-21, J=18.1), 6.16 (d, 1H, C-1, J=10.1), 7.33 (d, 1H, C-2, J=10.1). Anal. ($C_{27}H_{38}O_{10} \cdot H_2O$) C, H.

COMPOUND 11: HYDROCORTISONE-GALACTOSIDE

11 beta, 17 alpha-Dihydroxy-3,20-dioxopregna-4-en-21-yl beta-D-galactopyranoside.

Compound 11 was prepared from acetyl galactoside 20 as described for glucoside 5 from acetyl glucoside 16. After lyophilization, 95 mg (60%) of compound 11 was obtained; TLC: R_f 0.42 ($CHCl_3$/95% EtOH, 7:3); UV lambda(max): 242 nm (epsilon 15700); IR(KBr): 3450 (OH), 1660 (C=O), 1620 (C=C), 1080, 1033, 930, 896, 870 cm^{-1}; ^1H NMR delta 0.79 (s, 3h, C-18), 1.42 (s, 3H, C-19), 4.17 (d, 1H, C-1', J=7.6), 4.54 (ABq, 2H, C-21, J=18), 5.58 (s, 1H, C-4). Anal. ($C_{27}H_{40}O_{10} \cdot H_2O$) C, H.

COMPOUND 12: FLUDROCORTISONE-GALACTOSIDE

9 alpha-Fluoro-11 beta, 17 alpha-dihydroxy-3, 20-dioxopregna-4-en-21-yl beta-D-galactopyranoside.

Compound 12 was prepared from acetyl galactoside 21 as described for glucoside 5 from acetyl glucoside 16. After lyophilization, 0.11 g (71%) of compound 12 was obtained; TLC: R_f 0.49 ($CHCl_3$/95% EtOH, 7:3); UV lambda(max): 239 nm (epsilon 17700); IR(KBr): 3450 (OH), 1660 (C=O), 1620 (C=C), 1080, 1033, 930, 896, 870 cm^{-1}; ^1H NMR delta 0.78 (s, 3H, C-18), 1.50 (s, 3H, C-19), 4.20 (d, 1H, C-1', J=7.8), 4.55 (ABq, 2H, C-21, J=18), 5.70 (s, 1H, C-4). Anal. ($C_{27}H_{39}O_{10}F \cdot H_2O$) C, H.

COMPOUND 13: PREDNISOLONE-CELLOBIOSIDE

11 beta, 17 alpha-Dihydroxy-3,20-dioxopregna-1,4-dien-21-yl beta-D-cellobioside.

Compound 13 was prepared from acetyl cellobioside 22 as described for glucoside 5 from acetyl glucoside 16. After lyophilization, 86 mg (60%) of compound 13 was obtained; TLC: R_f 0.33 ($CHCl_3$/95% EtOH, 7:3); UV lambda(max): 242 nm (epsilon 15500); IR(KBr): 3450 (OH), 1680 (C=O), 1620 (C=C), 1170, 950, 898, 875 cm^{-1}; ^1H NMR delta 0.75 (s, 3H, C-18), 1.28 (s, 3H, C-19), 4.15 (d, 1H, C-1', J=7.6), 4.51 (ABq, 2H, C-21, J=18), 5.91 (s, 1H, C-4), 6.20 (d, 1H, C-1, J=10.2), 7.30 (d, 1H, C-2, J=10.1). Anal. ($C_{33}H_{48}O_{15} \cdot H_2O$) C, H.

IN VIVO TESTING

Male, Sprague-Dawley rats (ca 250 g) were maintained on laboratory rat chow and water ad lib. These rats were fasted overnight (16 hr.) prior to administration of glucoside or free steroid. Water bottles were removed from the cages at least 30 min prior to drug administration. Prednisolone glucoside, 2, (7.5 mg) or dexamethasone glucoside, 1, (7.5 mg) was administered by gastric intubation as a solution (0.5

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mL) of water/95% ethanol (3:1). Prednisolone, 4, (5.25 mg) or dexamethasone, 3, (5.1 mg) was administered as a solution (0.5 mL) of water/95% ethanol (1:1). After the appropriate interval of time -3, 4, 5 or 6 hr.- the animals were sacrificed by carbon dioxide anesthesia followed by thoractomy. The small intestine and cecum were removed and cut into segments. Contents were separated from the tissues by rinsing the segments with cold, 0.9% saline (5.0 mL). The contents were immediately diluted to 30 mL with methanol. The tissues were suspended in 0.01 M KH_2PO_4 (5.0 mL). Then an internal standard, either prednisolone, 4, or dexamethasone, 3, depending on the experimental steroid, was added to all the samples. Both the contents and tissues were then homogenized with a Polytron Homogenizer (Brinkman Inst. Co.) at med. speed for 1-2 min. The contents were then diluted to 40 mL total volume with methanol. The tissues were diluted to 25 mL total volume with methanol. All the samples were centrifuged (5,000g, 15 min) and then the supernatant solutions were passed through membrane filters (0.45 micrometers, Versapor 800). The samples (1.4 mL) were then diluted with 0.01 M KH_2PO_4 (0.6 mL) and 20 microliters of the resulting solution injected directly onto the HPLC column for analysis.

IN VITRO TESTING

Prednisolone glucoside, 2, (5.0 mg) or dexamethasone glucoside, 1, (5.0 mg) was incubated at 37°C in an 0.05 M acetate buffer, pH 5.0 (10.0 mL) with beta-glucosidase (EC 3.2.1.21, from almonds, one unit liberates 1.0 micromole of glucose from salicin per min at pH 5.0 at 37°C). Prednisolone glucoside, 2, and dexamethasone glucoside, 1, were treated with 50 and 500 units of enzyme, respectively. At various times, aliquots (0.1 mL) were removed and quenched with

methanol (9.9 mL). After centrifugation (5,000g, 10 min), the samples were diluted (1:1) with 0.01 M KH_2PO_4 and 20 microliters of the resulting solution injected directly onto the HPLC column for analysis.

Glucosides 1 and 2 (5.0 mg) were also incubated at 37°C with homogenized rat feces (0.5 g/10 milliliters 0.01 M phosphate buffer, pH 7.5). The feces were obtained from rats maintained on a high cellulose diet. See Shiau, S.Y., Chang, G.W. J. Nutr., 113:136 (1983). Aliquots (0.2 milliliters) were removed and quenched with MeOH (3.66 milliliters). After centrifugation (5,000g, 10 min), the samples were passed through membrane filters (0.45 micrometer pore, Versapor 450, Gelman Sciences, Inc.). They were then diluted (1:1) with 0.01 M KH_2PO_4. Twenty microliters of the resulting solution were injected directly onto the HPLC column for analysis.

IN VITRO METABOLISM

Rates of hydrolysis of three p-nitrophenyl-glycoside substrates, p-nitrophenyl-beta-D-glucoside (p-NP-glc), p-nitrophenyl-beta-D-galactoside (p-NP-gal), and p-nitrophenyl-beta-D-cellobioside (p-NP-cel), were measured in homogenized contents of the rat stomach, proximal small intestine (PSI), distal small intestine (DSI) and cecum. (The entire small intestine was divided into two, equal length segments to give PSI and DSI.) Gastrointestinal contents were obtained from male, Sprague-Dawley rats (300-400 g) which had been maintained on a stock diet (Purina rat chow) and water ad libitum. The intestinal contents of each section were pooled from four animals for each assay. Pooling the gut contents from four animals would be expected to lower the SD by a factor of two. Following removal, the contents were quickly weighed, then diluted to 100 milliliters (stomach, PSI, and DSI)

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or 200 milliliters (cecum) with cold 0.01 M phosphate buffer, pH 7.0. The diluted contents were homogenized with a Polytron homogenizer (Brinkman Instrument Co.) at medium speed for 1-2 min and the solution pH measured. Homogenates were then stored on ice (ca 30 min). Homogenates (0.8 milliliters of stomach and PSI, 0.2 milliliters of DSI, and 0.04 milliliters of cecum) were added to the appropriate substrate solution (0.01 M phosphate buffer, pH 7.0) to give 1.0 mM substrate (total volume: 2.25 milliliters). The reaction was run at 37°C in a shaking water bath. The reaction was stopped after 10, 20, or 30 min by addition of 0.2 N NaOH (0.25 milliliters). The amount of p-nitrophenol released was measured spectrophotometrically at 403 nm.

Rates of hydrolysis of glycoside prodrugs 1, 2, 5, 7, 9, 10, 11, 12, and 13 were measured in the same manner except that a higher concentration of each homogenate was used. Stomach and PSI contents were diluted to 50 mL with 0.01 M phosphate buffer, pH 7.0, DSI contents to 25 mL, and cecal contents to 200 mL, prior to homogenization. The homogenates (2.1 mL of stomach, PSI, and DSI and 1.7 mL of cecum) were added to the appropriate substrate solution (0.01 M phosphate buffer, pH 7.0) to give 1.0 mM substrate in a total volume of 2.5 mL. At various times up to 30 min, aliquots (0.3 mL) were removed and quenched with MeOH (4.7 mL). After centrifugation (5,000 g, 10 min), the samples were diluted (1:1) with 0.01 M KH_2PO_4 and 20 microliters of the resulting solution was injected directly onto the HPLC column for analysis.

$K_{M(app)}$ and V_{Max} Determinations. The $K_{M(app)}$-V_{max} for the hydrolysis of p-NP-glc and p-NP-gal were determined using pooled cecal homogenates (200 mL) as described above. A range of substrate (56-1000 micromolar; final volume 2.25 mL)

concentrations, spanning their apparent K_M, was used for each reaction. The amount of cecal homogenate used was 0.04 mL. Velocities were obtained, in duplicate, at 37°C in a shaking water bath and the reaction stopped by addition of 0.2 N NaOH (0.25 mL) after 15 min. Release of p-nitrophenol was measured spectrophotometrically at 403 nm. Eadie-Hofstee plots were used to determine the $K_{M(app)}$ (micromolar) and V_{max} (micromolar/min/g) of both reactions. The wet weight (g), measured immediately after removal and pooling, was used throughout.

The $K_{M(app)}$ and V_{max} were also measured from the hydrolysis of glycoside prodrugs 1, 2, 5, 7, 9, 10, 11 and 12. Again, cecal contents from four rats were pooled, weighed, diluted (100 mL, 0.01 M phosphate buffer, pH 7.0) and homogenized. A range of substrate concentrations (0.5-48 micromolar, final volume 2.5 mL) spanning the apparent K_M, was used for each reaction. The amount of cecal homogenate used was 0.8 mL. Reactions were run, in duplicate, at 37°C in a shaking water bath. After 15 min, the reactions were stopped by removing aliquots (0.3 mL) and quenching them with MeOH (4.7 mL). Following centrifugation (5,000g, 10 min), the samples were diluted (1:1) with 0.01 M KH_2PO_4 and 20 microliters of the resulting solution was injected directly onto the HPLC column for analysis. Again, Eadie-Hofstee plots were used to determine the $K_{M(app)}$ and V_{Max}.

Determination of Apparent Partition Coefficients.

The partitioning of prodrugs and free steroids between n-octanol and an aqueous phase (0.01 M phosphate buffer, pH 7.0) were determined at 37°C. Both octanol and buffer were saturated with the relevant aqueous or organic phas before use. Equal volumes (1.0 mL) of both phases wer used and agitated

for 30 min. The initial concentration of glycoside was 10 mM, dissolved in the aqueous phase. The intitial concentration of steroid was 10 mM dissolved in the organic phase. The amount of glycoside and free steroid in the aqueous phase at equilibrium was measured spectrophotometrically at 239 nm for the dexamethasone and fludrocortisone compounds and 242 nm for the prednisolone and hydrocortisone compounds. The concentration of glycoside or free steroid in the octanol phase was determined by difference.

Very generally, the invention discloses a colon-specific drug delivery system based on the use of a synthetic prodrug composition. The prodrug is comprised of the combination of an aglycone attached to a sugar by means of a glycosidic link. According to the invention, the aglycone is a drug composition, the sugar is a sugar recognizable as a substrate by bacterial glycosidases produced by colonic microflora, and the glycosidic link is a glycosidic link capable of being cleaved by the glycosidase enzymatic action of colonic microflora following recognition of the sugar as a substrate by the bacterial glycosidases. Also according to the invention, the prodrug combination is of sufficient size and hydrophilicity to allow it to pass through the mammalian gastrointestinal tract without being absorbed from the gaastrointestinal tract or without being significantly hydrolyzed by endogenous enzymes produced by the mammalian host. As a result, the prodrug will reach the area of the mammalian colon where the glycosidic link on the prodrug will be cleaved by the colonic bacterial glycosidases to release free drug most significantly to the colonic area f the bowel.

More specifically, the invention discloses a

colon-specific drug delivery system based on the use of a synthetic prodrug composition, the prodrug being comprised of an aglycone moiety attached to a sugar moiety by means of a glycosidic link thereby producing a drug glycoside.

The aglycone moiety of the prodrug composition useful in the colon-specific drug delivery system disclosed herein will preferably be comprised of a drug that is most efficacious when its adsorption or absorption is essentially limited to the area of the colon. Such drugs include steroid and antibiotic drugs useful in the treatment of inflammatory bowel disease. When these drugs are absorbable, they will generally be more lipophilic than hydrophilic, and will be small enough to pass through the gastrointestinal mucosa, since, as is well known, lipophilic substances generally penetrate membranes more readily then hydrophilic substances do, and smaller molecules penetrate more readily than larger ones. Steroid drugs, antibiotics and cancer chemotherapeutic agents are preferred aglycone moieties for use in the prodrugs of the present invention. Especially preferred are steroid drugs, including prednisolone, dexamethasone, hydrocortisone and fludrocortisone.

The sugar moiety of the prodrug composition useful in the colon-specific drug delivery system disclosed herein will be comprised of a sugar moiety recognizable as a substrate by glycosidases produced by bacteria present in the mammalian intestine. Since the hydrolytic action of these bacterial glycosidases is the mechanism by which the glycosidic bond, linking the sugar moiety to the aglycone, is cleaved, it is essential that the glycoside and/or the sugar moiety, or portions thereof, be recognizable as a substrate by these bacterial enzymes. It is also essential that the

sugar-drug combination, i.e. the drug glycoside, be of sufficient size and hydrophilicity to enable the prodrug to pass through the mammalian gastrointestinal tract without being significantly absorbed from the mammalian gastrointestinal tract or without being significantly hydrolyzed by endogenous enzymes produced by the mammalian host.

Although the principle glycosidases produced by the colonic microflora are beta-glycosidases, alpha-glycosidases are also produced. Thus both alpha and beta glycoses can be utilized as sugar moities in the synthetic drug glycosides disclosed herein. Since the beta-glycosidases are the principle colonic microfloral enzymes, beta-glycosides are preferred as prodrugs for use in the present colon-specific drug delivery system. However, those skilled in the art will recognize that certain alpha-glycosides can also be utilized.

The sugar moieties on the synthetic prodrugs will preferably be simple natural sugars. Preferred are natural monosaccharide, disaccharide and oligosaccharide hexoses and pentoses. Especially preferred are the natural monosaccharide hexoses D-glucose and D-galactose and the disaccharide D-cellobiose.

Since in the present invention the sugar moiety on the prodrug functions as a substrate for the bacterial glycosidases, those skilled in the art will recognize that modifications of these natural sugars are possible as long as the substrate specificity of the parent sugar molecules are preserved. For example, it is possible to substitute sulfur for oxygen on the sugar molecule. Such synthetic derivatives of the natural sugars are within the scope of this invention as long as the substrate specificity of the parent

compound remains intact.

Those skilled in the art will also recognize that the glycone, aglycone and glycosidic linkage can probably all be varied to improve or alter the rate and location of drug release. Such variations fall within the scope of the present invention. For example, the sugar residue could be altered by modifying functionalities (See Whitaker, J.R., Principles of Enzymology for the Food Sciences, Marcel Dekker, New York, N.Y. (1972) pp. 434-442), or an oligosaccharide carrier could be used to hinder the rate of hydrolysis in vivo. Slow hydrolysis of refractory prodrugs in the colon might prove to be an effective mechanism for sustained-release. Changing the aglycone, as demonstrated herein, can also alter delivery. Furthermore, the stereochemistry of the glycosidic link might be utilized to vary rates and sites of release. A sustained release system for the small intestine based on certain alpha-glycosides could be cleaved by digestive enzymes. Absorption would then be moderated by the rate of release in the small intestine, as well as the physicochemical properties of the parent drug.

The present prodrug delivery system is based on use of synthetic drug glycoside prodrug compositions from which active drugs are liberated following hydrolysis of the prodrugs by specific glycosidases produced by intestinal bacteria. Since in man such intestinal bacteria are normally found in the area of the colon (See Draser, B.S. and Hile, M.J., "Human Intestinal Flora", Academic Press: London (1974) pp. 54-71), use of the present prodrug delivery system will usually result in liberation of active drugs in that area of the intestine. However, those skilled in the art will realize that certain disease states (e.g., regional ileitis or Crohn's disease) can also cause

intestinal bacteria to accumulate in the normally sterile area of the small intestine. The accumulation occurs because, due to swelling and inflammation, ingested materials do not pass as quickly as they normally would through the small intestine. This slow-down in transit time leads to an "accumulation" of ingested material which in turn leads to an "accumulation" of bacteria that would not otherwise be found in this area of the intestine. In such cases, the present prodrug delivery system can be used to deliver active drugs to the diseased areas of the small intestine since such areas will normally coincide with the areas of the small intestine where the glycosidase producing colonic bacteria are accumulating.

It has been shown that the activity of glycosidic enzymes of the colon bacteria can be changed dramatically by diet. For example, in human subjects bean diets result in a large increase in alpha-galactosidase activity whereas oat bran diets increase beta-glucosidase activity. See Chang, G.W., Fukumoto, H. E., Gyory, C. P., Block, A. P., Kretsch, M. J. and Calloway, D. H., Fed. Proc. 38: 767 (1979) (Abstract). Since the drug delivery system of the present invention is based on substantially unique glycosidase activities of colonic microflora, and since the levels of the glycosidase enzymes of the colon bacteria can be controlled by simple dietary changes, physicians utilizing the colon-specific drug glycoside delivery system disclosed herein will have a further degree of control over their patient's treatment. For example, manipulation of glycosidase activity by diet may be very useful in standardizing glycosidase activity and also in raising enzyme activity in patients with a diseased colon where enzyme levels may be depressed.

To form a prodrug to be utilized in the

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present colon-specific drug delivery system, the invention teaches attachment of a sugar residue to the drug aglycone to create a synthetic drug glycoside. These drug glycosides can be synthesized by known chemical methods. See Igarashi, K., Adv. Carbohydr. Chem. Biochem. 34:243-283 (1977). Especially preferred as methods of preparing the drug glycosides disclosed herein are modifications of the Koenigs-Knorr reaction. See Meystre, C. and Miescher, K., Helv. Chim. Acta. 28:1153-1160 (1944); Koenigs, W. and Knorr, E., Ber. 34:957-981 (1901); and Igarashi, K., Adv. Carbohydr. Chem. Biochem. 34:243-283 (1977). In general, the procedure involves the treatment of a per-O-acylated glycosyl halide with an alcohol in the presence of a heavy-metal salt of an organic base as the acid acceptor. As used herein, the modified methods involve coupling a per-O-acylated glycosyl halide with an appropriate steroid in chloroform in the presence of silver carbonate as acid acceptor. See FIGURE 1. The acetyl protecting groups on the sugar residues of the drug glycosides are then removed by treatment with bases to yield synthetic drug glycosides.

Use of the modified Koenigs-Knorr reaction to prepare drug glycosides is illustrated herein with the preparation of glucoside 2 (and its acetyl precursor PREDTAGLU) and glucoside 1 (and its acetyl precursor DEXATAGLU). See Example I. As discussed further in Example II, the modified Koenigs-Knorr reaction has also been used to produce a variety of other drug glycosides useful in the drug delivery system of the present invention. These drug glycosides include: prednisolone-21-beta-D-galactoside, 10; dexam thasone-21-beta-D-galactoside, 9; hydrocortisone-21-beta-D-glucoside, 5; hydrocortisone-21-beta-D-galactoside, 11; fludrocortisone-21-beta-D-glucoside, 7;

fludrocortisone-21-beta-D-galactoside, 12. Example II further illustrates the preparations and use of drug glycosides consisting of a disaccharide coupled to a drug. Such drug glycosides are represented by prednisolone-21-beta-D-cellobioside, 13.

In utilizing the synthetic drug glycosides as prodrugs in the present colon-specific drug delivery system, the prodrug is administered orally or intragastrically to the mammalian host. The prodrug is then allowed to pass through the mammalian host's gastrointestinal system. Since the synthetic prodrug is larger and more hydrophilic than the parent drug, the prodrug is less permeable than the parent drug. In addition, since the glycosidic bond linking the glycose to the aglycone is a bond that will be substantially selectively cleaved by glycosidic bacterial enzymes produced by colonic microflora, the synthetic prodrug will pass through the gastrointestinal tract without being significantly absorbed from the gastrointestinal tract or without being significantly hydrolyzed by endogenous enzymes produced by the mammalian host. Once in the area of the colon, the prodrug will be acted upon by bacterial glycosidases, thus releasing free drug for adsorption to or absorption by the colonic mucosa.

In a preferred form of the present invention the synthetic prodrugs are comprised of the 21-yl beta-D-glucosides and galactosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone, and the 21-yl beta-D-cellobioside of prednisolone. Especially preferred is the steroid glycoside dexamethasone-21-beta-D-glucoside (1).

Synthesis of dexamethasone-21-beta-D glucosid , 1, and prednisolone-21-beta-D-glucoside, 2, using a modified Koenigs-Knorr reaction, is shown in

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Example I. In preparing these synthetic drug glycosides, the bromosugar, 2,3,4,6-tetra-O-acetyl-1-bromo-alpha-D-glucopyranose, was coupled with the appropriate steroid in chloroform in the presence of silver carbonate as acid acceptor. Acetyl glycoside products were isolated and then the acetyl protecting groups on the sugar residues of the glycosides removed by treatment with base.

The two synthetic drug glycosides were then used in the colon-specific drug delivery system disclosed herein. As shown more specifically in Example I, drug glycosides 1 and 2 were administered intragastrically to mammalian rat hosts. Analysis of the hosts' intestinal contents and tissues revealed that in this host, both drug glycosides 1 and 2 reached the colon within 4-5 hours, where they were rapidly hydrolyzed. Although delivery of dexamethasone (via glycoside 1) appeared to be more specific than that of prednisolone (via glycoside 2) in the rat host, both steroid drugs reached the area of the colon when administered via the colon-specific drug delivery system disclosed herein. (Nearly 60% of an oral does of glycoside 1 reached the cecum whereas less than 15% of glucoside 2 did.) In contrast, when the free drug steroids prednisolone and dexamethasone were administered orally, they were absorbed almost exclusively from the small intestine.

The influence of prodrug structure on specificity of glycoside/glycosidase based colon-specific drug delivery was studied by preparing seven additional steroid glycosides (See Example II), measuring their relative lipophilicities (See Example V) and hydrolyzing them with bacterial glycosidases from rat intestines (See Examples III and IV). Preparation of compounds 1 and 2 is outlined in Example

I. Preparation of the seven additional compounds is outlined in Example II. (The nine steroid glycosides are comprised of the 21-yl beta-D-glucosides and galactosides of dexamethasone, prednisolone, hydrocortisone and fludrocortisone, and the 21-yl beta-D-cellobioside of prednisolone.)

As illustrated in Examples III and IV, the nine deacetylated glycoside prodrugs, along with the p-nitrophenyl derivatives of beta-D-glucoside, galactoside, and cellobioside, were subjected to hydrolysis by the contents of the rat stomach, proximal small intestine (PSI), distal small intestine (DSI), and cecum. As the data in Example III demonstrate, all the prodrugs were hydrolyzed slowly by PSI and stomach contents, more rapidly by contents of the DSI, and most rapidly by cecal contents. However, the prodrugs themselves had very different susceptibilities to hydrolysis. Hydrolysis rates catalyzed by DSI contents decreased in the following order: prednisolone 21-yl beta-D-galactoside (10) > prednisolone 21-yl beta-D-glucoside (2) > prednisolone-21-yl beta-D-cellobioside (13) > dexamethasone 21-yl beta-D-galactoside (9) > dexamethasone 21-yl beta-D-glucoside (1). Hydrolysis of cellobioside 13 was only half that of glucoside 2 and one-fourth that of galactoside 10. Hydrolysis of all the prodrugs in cecal contents was rapid, with the exceptions of hydrocortisone 21-yl beta-D-glucoside (5) and fludrocortisone 21-yl beta-D-glucoside (7), which were hydrolyzed more slowly than the other glucoside prodrugs. Eadie-Hofstee plots were used to determine the $K_{M(app)}$ and V_{MAX} of the reactions. The Eadie-Hofstee plots suggested that bacterial beta-D-glucosidase activity in the colon may be more heterogeneous in nature than beta-D-galactosidase activity. See Example IV.

Since the physicochemical properties of the prodrug can influence the specificity of the present delivery system and since lipophilicity is very important in determining rates of penetration across biological membranes, gastrointestinal absorption as predicted by octanol-buffer partition coefficients was also investigated. More specifically, the relative lipophilicities of the prodrugs and free steroids were compared by measuring their octanol-buffer partition coefficients (P). Log P of the free steroids ranged from 1.54 to 1.73. Log P of the prodrugs ranged from 0.11 to 0.84, except for the logarithm of the P of cellobioside 13 which was considerably lower (-0.56). See Example IV.

Those skilled in the art will realize that the specificity of delivery of a glycoside prodrug to the lower intestine can be estimated from its rate of hydrolysis by DSI contents and its octanol-buffer partition coefficient since these parameters limit the amount of prodrug which can survive premature hydrolysis or absorption in the DSI. For example, under the assay conditions used in this study, glucoside 1 supported a specific activity of hydrolysis of 19 nmole/min/g in DSI contents and had a log P value of 0.59. When this prodrug was administered orally to rats, about half of the dose reached the cecum. Even more effective delivery could be expected of any prodrug which supports less hydrolysis by DSI contents and which has a lower log P value.

The data from the *in vivo* and *in vitro* tests indicate that use of a disaccharide such as cellobiose, or even a trisaccharide, as the hydrophilic moiety, can produce a prodrug which will be superior in some instances. Such oligosaccharide carriers might be ess ntial if smaller or more lipophilic drugs are to be

delivered to the large intestine. In addition, the in vitro data from Examples II-IV indicate that the relative rates of hydrolysis, and the relative lipophilicities can be used in conjunction with the in vivo data from Example I to enable one skilled in the art to estimate the site-specificity of glycoside prodrugs prior to extensive animal studies.

Thus it can be seen that the drug glycosides of the present invention have the property of undergoing bacterial cleavage of their glycosidic bond under conditions found in the gastrointestinal tract of mammals. The free drug liberated by such cleavage is absorbable through the colonic mucosa. Based on the art's teaching of the pharmacological efficacy of the free drugs, administration of the drug via the prodrug is thus shown to be possible.

Specific embodiments of the present invention are outlined in the following examples. Such examples are for illustrative purposes only and are not intended to limit the scope of the claims in any way.

EXAMPLE I

The teaching of the present invention makes it possible to construct a variety of synthetic drug glycosides useful in the disclosed colon-specific drug delivery system. This example compares the use of two such steroid glycosides, dexamethasone-21-beta-D-glucoside, (1), and prednisolone-21-beta-D-glucoside, (2), in the disclosed colon-specific delivery system.

Dexamethasone and prednisolone are steroid drugs useful in the treatment of inflammatory bowel disease. Prodrugs 1 and 2 are the respective drug glycosid s of these two steroid compounds. To test the efficacy of 1 and 2 in the colon-specific drug delivery system disclosed herein, the prodrugs were administered

intragastrically to rats. The intestinal contents and tissues were then analyzed to determine where the steroids were released and absorbed. Prednisolone and dexamethasone were also administered to compare the absorption of the drug glucosides with the free steroids. Both drug glucosides 1 and 2 were found to reach the colon in 4-5 hr., where they were rapidly hydrolyzed. Delivery of dexamethasone (via glucoside 1) to the rat lower intestine appeared to be more specific than that of prednisolone (via glucoside 2): 60% of an oral dose of glucoside 1 and 15% of an oral dose of glucoside 2 reached the cecum. In contrast, when the free steroids prednisolone and dexamethasone were administered orally, they were absorbed almost exclusively from the small intestine: less than 1% of the oral doses reached the cecum.

Glucosides 1 and 2 were prepared by glycosylation of dexamethasone and prednisolone using a modified Koenigs-Knorr reaction. See Meystre, C. and Miescher, K., Helv. Chim. Acta. 28:1153-1160 (1944); and Koenigs, W. and Knorr, E., Ber. 34:957-981 (1901). The bromosugar, 2, 3, 4, 6-tetra-O-acetyl-1-bromo-alpha-D-glucopyranose, was coupled with the appropriate steroid in carbon tetrachloride in the presence of silver carbonate as acid acceptor. See FIGURE 1. Acetyl glycoside products were isolated from the reaction mixture by column chromatography on reversed-phase (C-18) packing material. Yields were 38% for PREDTAGLU, 15, and 25% for DEXATAGLU, 14. These fair yields are typical for this reaction. See Igarashi, K., Adv. Carbohydr. Chem. Biochem. 34:243-283 (1977).

Proton NMR confirmed that the glucosides formed were beta linked. The anomeric proton (C-1') exhibited a doublet at 4.20 ppm for PREDTAGLU, 15, and

4.18 ppm for DEXATAGLU, 14. The coupling constants were 8 Hz for both compounds. These resonance signals indicate a trans-diaxial relationship between the vicinal C-1', 2' protons. See Williamson, D.G., Collins, D.G., Layne, D.S. and Bernstein, S., Biochemistry 8:4299-4304 (1969).

The acetyl protecting groups on the sugar residues of PREDTAGLU, 15, and DEXATAGLU, 14, were removed by treatment with 0.01 N sodium hydroxide. The ^1H NMR of these compounds again provided evidence of the stereochemistry at their anomeric carbons (beta-linked). Also, treatment of both glucoside 2 and glucoside 1 with commercial beta-glucosidase led to the removal of the glucose moiety in each case. Glucoside 2 was hydrolyzed several orders of magnitude faster than was glucoside 1. In addition, incubating these glucosides with homogenized rat feces resulted in extensive hydrolysis of each.

Separation of the glycosides from the free steroids was performed by HPLC. A typical chromatogram of the cecal contents of a rat given glucoside 1 intragastrically and sacrificed 6 hr. later is shown in FIGURE 2. Peak A is glucoside 1; Peak B is dexamethasone, 3; and Peak C is prednisolone, 4, which was added prior to homogenization as an internal standard. (The Altex 5 micrometer Ultrasphere, C-18 column was eluted with MeOH/0.01 M KH_2PO_4 (56.5:43:5) at a flow rate of 1.2 mL/min.)

The recovery of glucoside 1 and free steroid 3 from the small intestine and cecum at various times following oral administration of glucoside 1 is given in Table I, supra. As the data in the table illustrate, after 3 and 4 h, glucoside 1 was recovered primarily in the lower small intestine. By 5 h, very littl f glucoside 1 was observed in either the small

intestine or cecum. (At the same time, large amounts of steroid 3 were recovered from the cecum.) However, as glucoside 1 passed from the lower small intestine into the cecum, the free drug was released rapidly. The fact that some free steroid was detected in the small intestine at the times tested indicated that some hydrolysis occurred before the prodrug reached the cecum or colon.

The recovery of steroid glucosides and free steroids from the intestinal contents and tissues is also shown graphically in FIGURE 3. In that figure, recovery of glucoside 1, (DEXAGLU), and dexamethasone 3, (DEXA), from rats given 7.5 mg of glucoside 1 at 0 hr are shown in panels A and B. Recovery of glucoside 2 (PREDGLU) and prednisolone 4 (PRED) from animals given 7.5 mg of glucoside 2 at 0 hr are shown in panels C and D. Data are given as means ±SEM (n=4). Solid circle and triangle symbols indicate intestinal contents; open circle and triangle symbols indicate intestinal tissues.

The results reveal that overall, the delivery of glucoside 1 and subsequent release of steroid 3 in the rat cecum was quite specific. At 4 h, 59% of the administered dose of glucoside 1 was recovered from the lower small intestine contents unhydrolyzed. If all this glucoside passed into the cecum, then nearly 60% of the dose would have been delivered specifically to the cecum. At 5 h, an average of 2.24 mg (or an equivalent of 44% of the administered dose) was recovered in the cecum as free steroid. The difference (59% vs. 44%) was probably due to absorption of free drug by the cecal mucosa following hydrolysis of the prodrug in the cecum.

The recovery of glucoside 2 and free steroid 4 from the small intestine and cecum at various times

following oral administration of glucoside 2 is given in Table II supra. Recovery of glucoside 2 after 3 and 4 h from the small intestine was much lower than that for glucoside 1. By 5 h, some free steroid was found in the cecum, however the specificity was quite low. Free steroid 4 was detected in the small intestine at all time points tested, again indicating the presence of glycosidases in the rat small intestine. The recovery of glucoside 2 and steroid 4 from the intestinal contents and tissues is shown graphically in panels C and D of FIGURE 2.

The results indicate that delivery of glucoside 2 was less efficient than that of glucoside 1. Only 14.8% of the administered dose of glucoside 2 could be recovered as such from the lower small intestine after 4 h. Therefore, only about 15% of the dose could have been delivered to the cecum. By 5 h, an average of 0.57 mg of steroid 4 (or an equivalent of 11% of the administered dose) was recovered in the cecum. Again, the difference (14.8% vs. 11%) is probably due to absorption of steriod 4 into the systemic circulation following hydrolysis in the cecum.

No glucoside or free steroid was recovered from the colon of those animals tested. This was probably due to slow transit times and the fact that the time points tested following administration did not allow for any released steroid to pass into the rat colon. Transit times in this experiment were slower, but still close to the value of 6.6 ± 0.4 h reported for passage through the alimentary canal of rats fed a stock diet. See Williams, V.J., Senior, W., Aust. J. Biol. Sci., 35:373 (1982).

The specificity of drug release was evaluated further by comparing the difference in free steroid recovered in the small intestine and in the cecum. A

paired t-test indicated that the preferential release of free steroid 3 in the cecum over that in the small intestine was statistically significant ($t = 2.32$, $p < 0.025$). A similar analysis of recoveries of steroid 4 showed that the preferential release of 4 in the cecum was not quite statistically significant ($t = 1.72$, $0.05 < p < 0.10$).

Intestinal transit times varied greatly, and in many cases the administered dose did not reach the cecum by the time of sacrifice. When these animals were excluded from the statistical calculations, the specificity of release is greater for both steroids 2 and 4. Measurable amounts of glucoside 1 reached the cecum in eleven of the sixteen animals tested. Analysis of data from only these eleven animals showed that the preferential release of steroid 3 had high statistical significance ($t = 3.17$, $p < 0.01$). For glucoside 2, it was found that the administered dose reached the cecum in eight of sixteen animals tested. Data from these eight animals indicated that the preferential release of steroid 4 was statistically significant ($t = 3.94$, $p < 0.005$). However, the combined total recoveries of glucoside 2 and steroid 4 at 4 and 5 h was very low. Therefore the efficiency of drug delivery to the cecum was very low, despite the calculated significance.

Control experiments in which unmodified steroids 3 and 4 were administered showed that they were absorbed almost completely from the small intestine. These data are shown in FIGURE 4. In that figure, recovery of steroid from animals given 5.25 mg of dexamethasone (DEXA), 3, is shown in panel A; recovery of steroid from animals given 5.10 mg of prednisolone (PRED), 4, is shown in panel B. Data points are means ± SEM (n=3) from intestinal contents,

shown as solid circles, and tissues, shown as open circles.

The system illustrated in this example is based on the release of anti-inflammatory steroids from poorly absorbed steroid glycosides in the rat cecum. Despite the obvious anatomical differences between the laboratory rat and man, the rat cecum can be considered to be a satisfactory model for the proximal colon of man. Both organs are recipients of digesta from the small intestine and both are sites of large bacterial populations and extensive microbial activity. Therefore, the term "lower intestine" is used herein for either the combined rat cecum and colon or the human colon with its poorly defined cecal area.

While the rat model is useful, it suffers from the problem of a relatively high bacterial population and a subsequently high level of glycosidase activity that is present in the stomach, upper small intestine, and lower small intestine. For example, there are an average of $10^{7.7}$, $10^{6.9}$, and $10^{7.7}$ microorganisms/g wet weight in the rat stomach, upper small intestine, and lower small intestine, respectively. In contrast, the bacterial population in man's stomach and small intestine is much lower. There are only an average of 10^{0}, $10^{2.6}$, and $10^{4.2}$ microorganisms/g wet weight residing in the human stomach, upper small intestine, and lower small intestine, respectively. See Drasar, B.S. and Hill, M.J., "Human Intestinal Flora", Academic Press: London (1974) pp. 54-71, and Hawksworth, G., Drasar, B.S. and Hill, M.J., J. Med. Microbiol. 4:451 (1971). Bacteroides and Bifidobacteria are the bacterial species comprising the majority of microorganisms in the gastrointestinal system of both the laboratory rat and man. In addition, both species have been shown to produce measurable quantities of

beta-glucosidase in vivo. See Hawksworth et al., supra.

Despite the high level of microbial activity in the rat upper intestine, glucoside 1 showed remarkable specificity towards the lower intestine. This prodrug should be even more specific when used in man because the microbial activity in human stomach and small intestine is much lower than that of the rat. Sulfasalazine, a prodrug used successfully in man, requires activation by colonic microflora. See Peppercorn, M.A. and Goldman, P., J. Pharm. Exp. Ther. 181:55 (1972), and Peppercorn, M.A. and Goldman, P., Gastroenterology 64:240 (1973). Sulfasalazine works on much the same principle as does the present glycoside/glycosidase delivery system. Therefore, based on the similarities between these two prodrug delivery systems, and the degree of specificity of glucoside 1 demonstrated in the rat model, it is likely that certain drugs can be effectively delivered to the colon of man via glycoside prodrugs.

It is worth noting that the relatively poor performance of glucoside 2 in the rat model could be due to several factors. Although it is possible that glucoside 2 was absorbed more extensively from the stomach and small intestine than was glucoside 1, it was more likely that glucoside 2 was hydrolyzed to a greater extent in the stomach and small intestine than was glucoside 1. Commercial beta-glucosidase was much more active towards glucoside 2 than towards glucoside 1. Similar factors may be functioning in the rat gastrointestinal tract.

EXAMPLE II

This example illustrates synthesis of seven additional drug glycosides useful in the colon-specific drug delivery system of the present invention.

Using the modification of the Koenigs-Knorr reaction discussed supra, a number of additional drug glycosides have been synthesized. Some of these drug glycosides are listed below. The compounds in parentheses are the protected glycoside products produced in the first step of the modified synthesis. See FIGURE 1. The protecting groups (acetyl functions) were removed with base to give the glycosides preceding the compounds in parentheses. The compounds include: prednisolone-21-beta-D-galactoside, 10, (and pred.-21-yl 2,3,4,6-tetra-O-aceto-beta-D-galactoside, 19); dexamethasone-21-beta-D-galactoside, 9, (and dexa.-21-yl 2,3,4,6-tetra-O-acetyl-beta-D-galactoside, 18); hydrocortisone-21-beta-D-glucoside, 5, (and hydrocort.-21-yl 2,3,4,6-O-tetra-O-acetyl-beta-D-glucoside, 16); hydrocortisone-21-beta-D-galactoside, 11, (and hydrocort.-21-yl 2,3,4,6-tetra-O-acetyl-beta-D-galactoside, 20); fludrocortisone-21-beta-D-glucoside, 7, (and fludrocort.-21-yl 2,3,4,6-tetra-O-acetyl-beta-D-glucoside, 17); fludrocortisone-21-beta-D-galactoside, 12, (and fludro-21-yl 2,3,4,6-tetra-O-acetyl-beta-D-galactoside, 21), and prednisolone-21-beta-D-cellobioside, 13, (and prednisolone-21-yl heptaacetyl-beta-D-cellobioside, 22).

Proton NMR spectroscopy of the acetyl glycosides indicated a beta-linkage at their anomeric carbons. All the compounds exhibited a doublet at approximately 4.2 ppm for the anomeric proton with coupling constants ranging from 7.2 to 8.0 Hz. These resonance signals indicate a trans-diaxial relationship between the C-1',2' protons. See Williamson, D.G., Collins, D.C., Layne, D.S., Conrow, R.B., and Bernstein, S., Biochemistry 8:4299 (1969).

Removal of the acetyl protecting groups on the

sugar residues was accomplished by base catalyzed hydrolysis using 0.01 N NaOH in MeOH. Yields ranged from 60 to 83% for this step. ^1H NMR spectroscopy confirmed that the free glycosides were still beta-linked.

EXAMPLE III

Results from the study of the present glycoside/glycosidase based delivery system in the laboratory rat indicate that certain anti-inflammatory steroids can be delivered to the lower intestine with varying degrees of specificity, depending on the aglycone. To better understand the factors controlling specificity, and to demonstrate the behavior of additional drug glycosides in the mammalian gastrointestinal tract, the kinetics of release of aglycones from three p-nitrophenyl-glycosides and nine steroid glycoside prodrugs were measured using freshly prepared homogenates from contents of the rat stomach, proximal small intestine (PSI), distal small intestine (DSI), and cecum.

More specifically, total activities (micromoles/min) and specific activities (nmoles/min/g) of native enzymes were first measured in stomach, PSI, DSI, and cecal content homogenates using three p-nitrophenyl-glycoside substrates. This was accomplished by following the release of p-nitrophenyl from p-nitrophenyl-beta-D-glucoside (p-NP-glc) via beta-D-glucosidase, p-nitrophenyl-beta-D-galactoside (p-NP-gal) via beta-D-galactosidase, and p-nitrophenyl-beta-D-cellobioside (p-NP-cel) via beta-D-cellobiosidase and beta-D-glucosidase. Results of these measurements are shown in Table III. Release of p-nitrophenol from all three substrates in all four segments tested indicated the presence of glycosidase activity all along th rat gastrointestinal tract.

Total activities of each glycosidase were generally lowest in the stomach and PSI, higher in the DSI, and highest in the cecum. Specific activities of the three glycosidases followed the same general pattern, with highest activities found in the cecum. In addition to the gradient of glycosidase activity along the gastrointestinal tract, there were differences in enzyme levels. Specific activity of cecal beta-D-galactosidase was about four times that of cecal beta-D-glucosidase, and about sixteen times that of cecal beta-D-cellobiosidase.

Total activities and specific activities for hydrolysis of all nine glycoside prodrugs disclosed in Examples I and II were also measured. Results of those measurements are given in Tables IV (glucosides 1, 2, 5, 7) and V (galactosides 9, 10, 11, 12, and cellobioside 13). The tables are shown supra. Total and specific activities for the hydrolysis of all prodrugs were relatively low in the stomach and PSI contents. They increased in the DSI and were highest in the cecal content homogenates. This pattern follows that found for the hydrolysis of the p-NP-glycosides; however, in all homogenates tested, total and specific activities for hydrolysis of each type of prodrug (glucoside, galactoside, and cellobioside) were considerably lower than were those of the corresponding p-NP-glycosides.

The data indicate that hydrolysis of all prodrugs was relatively slow when incubated with homogenates of contents from the stomach and PSI, faster in the DSI homogenates, and fastest in the cecum. Loss f prodrugs through hydrolysis in the stomach and PSI is probably negligible. Transit through this portion of the rat gastrointestinal tract is quite rapid: transit times can b as low as 40 min.

This combination of low enzyme activity and rapid transit in the rat stomach and PSI means that specificity of delivery is probably a function of glycosidase activity and residence time in the DSI. Transit slows considerably in the DSI, increasing the possibility of premature hydrolysis and less specific drug-delivery to the rat cecum.

Differences in total and specific activities became apparent when each prodrug was incubated with the homogenates of the DSI contents. Dexamethasone prodrugs 1 and 2 were more resistant to hydrolysis than the other prodrugs. Of the two glucosides tested *in vivo*, glucoside 1 was found to be hydrolyzed about three times slower in the homogenates of the DSI contents than was glucoside 2. As shown in the animal tests included in Example I, glucoside 1 was delivered to the rat lower intestine about four times more specifically than was glucoside 2 (59% for 1 and 14% for 2). Therefore, there is a rough correlation between total and specific activities in homogenates of DSI contents, and specificity of delivery observed *in vivo*. Because the other prodrugs were all hydrolyzed to much greater extent in DSI homogenates, they may not be delivered to the lower intestine as specifically as glucoside 1.

All the prodrugs except glucosides 5 and 7 were hydrolyzed much faster by cecal contents than by DSI contents. The galactosides were hydrolyzed more rapidly by cecal homogenates than were their glucoside counterparts. Thus, any prodrug reaching the cecum following oral administration would be expected to rapidly liberate the pharmacon as desired, with the possible exception of glucosides 5 and 7. However, the galactoside prodrugs would probably release significant amounts of their free steroids in the DSI, prior to

reaching the lower intestine. Therefore, the galactoside prodrugs described herein would probably be poor candidates for drug delivery to the rat cecum. It should be noted that the human intestine has a much sharper gradient of bacterial colonization; compounds which are not delivered specifically in the rat may be in the human intestine. Furthermore, there may be applications in which it is desirable to deliver a drug to the DSI.

When compounds 13, 10 and 2 were incubated in DSI or cecal homogenates, the rate of release of prednisolone (4) from prednisolone-cellobioside (13) was much slower than that of steroid 4 from either glucoside 2 or galactoside 10. As a result, delivery of steroid 4, via cellobioside 13, to the rat cecum would probably still not be as specific as that of dexamethasone (3), via prodrug 1 or 9. However, the prednisolone-glycosides were the most enzymatically labile prodrugs investigated. A cellobioside derivative of any of the other three steroids would probably improve their specificity of delivery. Release of steroid 4 from cellobioside 13 in the rat cecum would probably be rapid, approximately the same as was observed *in vivo* for release of steroid 3 from glucoside 1. Slow release of steroid 4 from cellobioside 13 is probably due to the fact that the rate of hydrolysis by beta-D-cellobiosidase is slower than the two step hydrolysis by beta-D-glucosidase.

EXAMPLE IV

$K_{M(app)}$ and V_{Max} Determinations.

The K_M-V_{Max} data for hydrolysis of the p-nitrophenyl-beta-D-glucoside (p-NP-glc), p-nitrophenyl-beta-D-galactoside (p-NP-gal), and the glucoside and galactoside prodrugs are given in Table VI.

Eadie-Hofstee plots were used to determine the $K_{M(app)}$ and V_{MAX} of the enzyme reactions. The Eadie-Hofstee plots (of the relationship V vs V/[S]) for hydrolysis of p-NP-glc and p-NP-gal in homogenates of pooled cecal contents from four animals are presented in Figures 5 and 6. At lower substrate concentrations, the plot of the velocity-substrate relationship for hydrolysis of p-NP-glc deviated from linearity. Hydrolysis of p-NP-gal was, however, essentially linear.

In calculating the K_M and V_{Max} values for hydrolysis of p-NP-glc, p-NP-gal, and the glucoside and galactoside prodrugs, it was found that the beta-D-glucosidase activity may be more heterogeneous in nature than beta-D-galactosidase activity. This was seen in the Eadie-Hofstee plots, as shown in Figures 5 and 6, and may reflect the production of different beta-D-glucosidases by the many bacterial species living in the large intestine.

EXAMPLE V

Partition coefficients, often measured between n-octanol and an aqueous phase, have proved very useful in correlating lipophilicity with absorption patterns of compounds absorbed by passive diffusion from the gastrointestinal tract. See Leo, A., Hansch, C., and Elkins, D., Chem. Rev. 71:525 (1971). Therefore, partition coefficients of the prodrugs and the free steroids were measured.

More specifically, the apparent n-octanol-buffer (0.01 M phosphate buffer, pH 7.0) partition coefficients (P) were measured at 37°C. The results of these measurements, expressed as log P, are given in Table VII. Cellobioside 13 had the lowest log P (-0.56) of any of the prodrugs tested. The galactoside prodrugs all had lower log P values than

the corresponding glucoside prodrugs. As expected, the log P values for the free steroids were much greater than those of the glycosides.

The effect of incorporating a hydrophilic moiety (i.e., glucose) into dexamethasone is shown in Example I. More specifically, the data contained therein show that following oral administration of a glucose/dexamethasone drug glycoside (glucoside 1), 78% of the dose was recovered intact from the animals' intestinal lumen 3 h later; in contrast, only 3.9% of an oral dose of steroid 3 was recovered 3 h later. Thus, attaching a hydrophilic glucose moiety to steroid 3 drastically impeded its absorption. This is reflected in the difference in partition coefficients (log P) of glucoside 1 (0.59) and steroid 3 (1.72). Because the log P of glucoside 2 was even lower than that of glucoside 1, it appears that the poorer specificity of delivery of glucoside 2 in the rat model was due primarily to premature release of the drug in the upper intestine rather than absorption from the gastrointestinal lumen prior to reaching the cecum.

TABLES

The following tables are referred to infra:

Table I. Recovery of glucoside 1 and steroid 3 from the small intestine and cecum at various times after administration of 7.5 mg of glucoside 1.

time (h)	small intestine		cecum	
	1 (glucoside)	3 (steroid)	1 (glucoside)	3 (steroid)
3	5.61 mg[a]	0.13 mg	0.21 mg	0.09 mg
4	5.00	0.11	0.02	0.05
5	0.24	0.12	0.23	2.24
6	0.94	0.18	0.04	1.66

[a] values represent the average of 4 animals.

Table II. Recovery of glucoside 2 and free steroid 4 from the small intestine and cecum at various times after administration of 7.5 mg of glucoside 2.

time (h)	small intestine		cecum	
	2 (glucoside)	4 (free steroid)	2 (glucoside)	4 (free steroid)
3	1.57 mg[a]	0.30 mg	0.0 mg	0.0 mg
4	1.73	0.18	0.0	0.0
5	0.19	0.09	0.0	0.57
6	0.18	0.03	0.06	0.29

[a] values represent the average of 4 animals.

Table III. Hydrolysis of p-nitro phenyl-glucoside, p-nitro phenyl-galactoside, and p-nitro phenyl-cellobioside by the Contents of Different Segments of Rat Intestine.[a]

Intestinal segment	Substrate					
	p-NP-glc		p-NP-gal		p-NP-cel	
	Tot. act.	Sp. act.	Tot. act.	Sp. act.	Tot. act.	Sp. act.
stomach[b]	0.08	72.2	0.70	57.8	0.35	34.2
PSI[c]	0.15	43.2	0.20	58.3	0.05	7.2
DSI	0.65	86.6	3.6	425	0.25	26.0
cecum	9.1	454	30.8	1620	2.6	96.5

[a] Tot. act.: activity of contents of the entire intestinal segment, expressed as micromole/min. Sp. act.: specific activity of contents of the intestinal segment, expressed as nmoles/min/g wet weight.

[b] pH of stomach homogenates was ca 5.0.

[c] pH of PSI, DSI, and cecal homogenates was 7.0.

Table IV. Hydrolysis of Glucoside Prodrugs 1, 2, 5, and 7 by the Contents of Different Segments of Rat Intestine.[a]

Intestinal segment	Prodrug 1		2		5		7	
	Tot. act.	Sp. act.	Tot. act.	Sp. act.	Tot. act.	Sp. act.	Tot. act.	Sp. act.
stomach	0.12	6.8	0.12	6.8	0.09	5.5	0.14	7.7
PSI	0.07	11.0	0.07	12.2	0.10	15.9	0.08	12.3
DSI	0.34	19.3	1.0	56.8	0.70	39.2	0.43	33.0
cecum	3.5	141	6.6	265	0.76	30.5	1.4	42.0

[a] Measured by following the release of the free steroid by HPLC. Abbreviations and units are the same as those in Table II.

Table V. Hydrolysis of Galactoside Prodrugs 9, 10, 11, 12, and Cellobioside Prodrug 13 in Contents of Different Segments of Rat Intestine.[a]

Intestinal segment	Prodrug 9		10		11		12		13[b]	
	Tot. act.	Sp. act.	Tot. act.	Sp. act.	Tot. act.	Sp. act.	Tot. act.	Sp. act.	Tot. act.	Sp. act.
stomach	0.004	2.0	0.19	12.1	0.02	12.5	0.01	7.0	0.01	7.5
PSI	0.004	11.7	0.23	49.3	0.02	42.5	0.01	12.5	0.11	26.0
DSI	0.41	29.3	1.72	122	1.6	110	0.80	56.7	0.64	32.5
cecum	6.5	322	13	665	11.9	592	12.9	642	2.2	109

[a] Measured by following the release of the free steroid by HPLC. Abbreviations and units are the same as in Table I.

[b] Expressed as release of free steriod 4.

Table VI. $K_{m(app)}$ (micromolar) and V_{max} (micromolar/min/g) for Hydrolysis of p-NP-glc, p-NP-gal, and Prodrugs 1, 2, 5, 7, 9, 10, 11, and 12.[a]

substrate	$K_{m(app)}$	V_{max}
p-NP-glc[b]	360	697
p-NP-gal[b]	166	1233
glucoside 1[c]	2.5	2.2
glucoside 2[c]	4.5	2.6
glucoside 5	5.7	2.6
glucoside 7	4.4	2.4
galactoside 9	13.3	3.9
galactoside 10	20.0	10.3
galactoside 11	16.7	10.2
galactoside 12	33.3	20.6

a Measurements made in pooled cecal content homogenates.

b Reaction followed by measuring the release of p-nitrophenol spectrophotometrically at 403 nm.

c Measured by following the release of free steroid using HPLC.

Table VII. Apparent n-Octanol-Buffer Partition Coefficients (Log P).[a]

compd	Log P
glucoside 1	0.59
glucoside 2	0.27
glucoside 5	0.44
glucoside 7	0.84
galactoside 9	0.49
galactoside 10	0.11
galactoside 11	0.15
galactoside 12	0.25
cellobioside 13	-0.56
steroid 3[b]	1.72
steroid 4[c]	1.55
steroid 6[d]	1.54
steroid 8[e]	1.73

[a] Agitated for 30 min. at 37°C with concentration determined in the aqueous phase.

[b] Lit. (Leo, A., Hansch, C. and Elkins, D., Chem. Rev. 71:525 (1971)) values: 1.90, 1.59 (both using diethyl ether as organic phase).

[c] Lit. (Leo, et al., supra, value: 1.42.

[d] Lit. (Leo, et al., supra, values: 1.53, 0.96 (diethyl ether), 0.89 (benzene), 1.93 (iso-butyl alcohol).

[e] Lit. (Leo, et al., supra, value: 1.68.

The foregoing description and accompanying examples demonstrate the efficacy of a colon-specific drug delivery system based on the use of a synthetic drug glycoside prodrug composition which, when ingested by a mammal, undergoes reaction with colonic microflora to release a free drug capable of being adsorbed to or absorded by the colonic mucosa. The present drug delivery system combines the convenience of oral administration with the specificity of topical application. It is especially useful for the treatment of inflammatory bowel disease.

The invention also provides a method of making a colon-specific prodrug comprising forming a glycosidic link between a sugar and an aglycone wherein said sugar is a sugar recognizable as a susbtrate by bacterial glycosidases produced by colonic microflora and said glycosidic link is a glycosidic link capable of being cleaved by the glycosidase enzymatic activity of colonic microflora following recognition of said sugar as a substrate by said bacterial glycosidases, and said aglycone is a drug such that the resulting glycoside is of sufficient size and hydrophilicity to allow it to pass through the mammalian gastrointestinal tract without being significantly absorbed from the gastrointestinal tract or without being significantly hydrolyzed by endogenous enzymes produced by the mammalian host so that said prodrug can reach the area of the mammalian colon where said glycosidic link can be cleaved by said bacterial glycosidases to release free drug to the area of the colon.

Further included in the invention is a prodrug formulation comprising a prodrug of the invention or a glycoside of the invention, in either case formulated for pharmaceutical or veterinary use. Such formulation will be in accordance with standard practice in the art, e.g.

the use of the appropriate unit dosage forms.

The invention further provides a method of making a glycoside which comprises forming a glycosidic link between a sugar and an aglycone wherein said sugar is a sugar recognizable as a substrate by bacterial glycosidases produced by colonic microflora and said glycosidic link is a glycosidic link capable of being cleaved by the glycosidase enzymatic activity of colonic microflora following recognition of said sugar as a substrate by said bacterial glycosidases, and said aglycone and sugar are chosen such that the resulting glycoside is not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host but is capable of passing substantially unabsorbed through the gastro-intestinal tract to reach the colon.

Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications fall within the scope of the inventive concept.

CLAIMS:

1. A prodrug for use in a colon-specific drug delivery system comprising an aglycone attached to a sugar by means of a glycosidic link wherein said aglycone is a drug and said sugar is a sugar recognizable as a substrate by bacterial glycosidases produced by colonic microflora and said glycosidic link is a glycosidic link capable of being cleaved by the glycosidase enzymatic activity of colonic microflora following recognition of said sugar as a substrate by said bacterial glycosidases, said prodrug further being of sufficient size and hydrophilicity to allow it to pass through the mammalian gastrointestinal tract without being significantly absorbed from the gastrointestinal tract or without being significantly hydrolyzed by endogenous enzymes produced by the mammalian host so that said prodrug can reach the area of the mammalian colon where said glycosidic link can be cleaved by said bacterial glycosidases to release free drug to the area of the colon.

2. A prodrug according to claim 1, wherein said aglycone is a steroid drug and said sugar is a simple sugar.

3. A prodrug according to claim 2, wherein said steroid drug is prednisolone, dexamethasone, hydrocortisone or fludricortisone; said simple sugar is D-glucose, D-galactose or D-cellobiose; and said glycosidase activity of said colonic microflora is glycosidase activity produced by bacterial glycosidases which are beta-galactosidases, alpha-galactosidases, beta-galactosidases or beta-cellobiosidases.

4. A colon-specific prodrug comprised of a drug glycoside capable of being essentially cleaved by glycosidase enzymatic activity of colonic microflora but not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host thus enabling the most significant amounts of free drug to be released in the area of the colon following cleavage of the drug glycoside by glycosides produced by the colonic microflora.

5. A prodrug as claimed in claim 4 which is a drug-beta-D-glycoside.

6. A glycoside which is prednisolone-21-beta-D-glucoside (PREDGLU), dexamethasone-21-beta-D-glucoside (DEXAGLU), prednisolone-21-beta-D-galactoside, dexamethasone-21-beta-D-galactoside, hydrocortisone-21-beta-D-glucoside, hydrocortisone-21-beta-D-galactoside, fludrocortisone-21-beta-D-glucoside, fludrocortisone-21-beta-D-galactoside or prednisolone-21-beta-D-cellobioside.

7. A method of making a colon-specific prodrug comprising forming a glycosidic link between a sugar and an aglycone wherein said sugar is a sugar recognizable as a substrate by bacterial glycosidases produced by colonic microflora and said glycosidic link is capable of being cleaved by the glycosidase enzymatic activity of colonic microflora following recognition of said sugar as a substrate by said bacterial glycosidases, and said aglycone is a drug such that the resulting glycoside is of sufficient size and hydrophilicity to allow it to pass through the mammalian gastrointestinal tract without being significantly absorbed from the gastrointestinal tract or without being significantly hydrolyzed by endogenous enzymes produced by the mammalian host so that said prodrug can reach the area of the mammalian colon where said glycosidic link can be cleaved by said bacterial glycosidases to release free drug to the area of the colon.

8. A method as claimed in claim 7 further defined by the specific features of claim 2 or claim 3 or wherein the resulting glycoside is one claimed in claim 6.

9. A prodrug formulation comprising a prodrug as as claimed in any one of claims 1 to 5 or a glycoside as claimed in claim 6, in either case formulated for pharmaceutical or veterinary use.

10. A method for delivering a compound to the

mammalian intestine comprising administering to a mammalian hose, through said host's gastrointestinal tract, a synthetic glycoside comprising an aglycone attached to a sugar by means of a glycosidic link wherein said aglycone is the said compound and said sugar is a sugar recognizable as a substrate by bacterial glycosidases produced by mammalian intestinal microflora and said glycosidic link is a glycosidic link capable of being cleaved by the glycosidase enzymatic activity of mammalian intestinal microflora following recognition of said sugar as a substrate by said bacterial glycosidases, said glycoside further being of sufficient size and hydrophilicity to allow it to pass through the mammalian gastrointestinal tract without being significantly absorbed from the gastrointestinal tract or without being significantly hydrolyzed by endogenouse enzymes produced by the mammalian host so that said glycoside can reach the mammalian intestine where said glycosidic link can be cleaved by said bacterial glycosidases to release the free compound to the area of the intestine.

11. A method of making a glycoside which comprises forming a glycosidic link between a sugar and an aglycone wherein said sugar is a sugar recognizable as a substrate by bacterial glycosidases produced by colonic microflora and said glycosidic link is a glycosidic link capable of being cleaved by the glycosidase enzymatic activity of colonic microflora following recognition of said sugar as a substrate by said bacterial glycosidases, and said aglycone and sugar are chosen such that the resulting glycoside is not capable of being significantly hydrolyzed by endogenous enzymes produced by the mammalian host but is capable of passing substantially unabsorbed through the gastrointestinal tract to reach the colon.

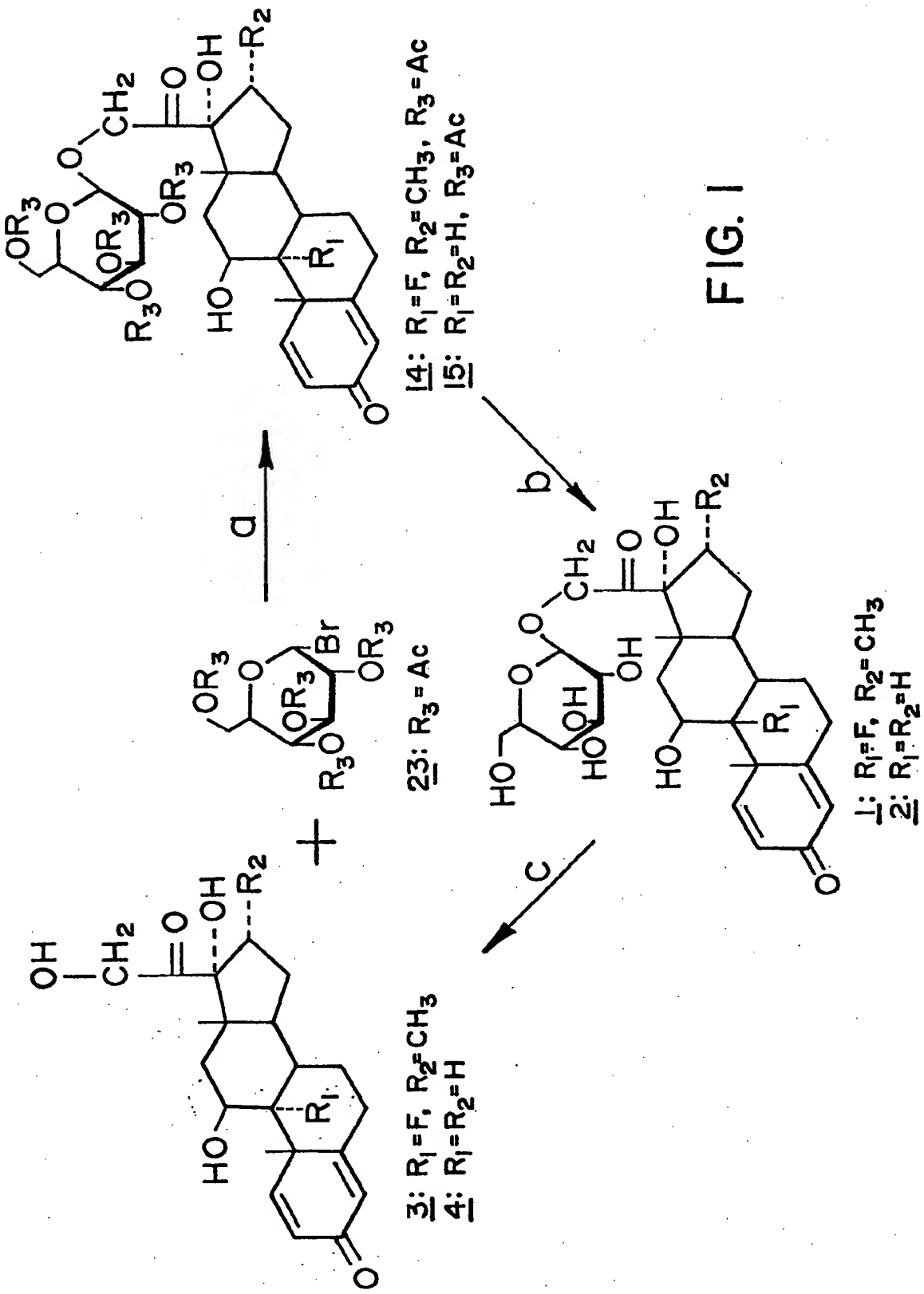
a
b
c
14: R1=F, R2=CH3, R3=Ac
15: R1=R2=H, R3=Ac
23: R3=Ac
1: R1=F, R2=CH3
2: R1=R2=H
3: R1=F, R2=CH3
4: R1=R2=H

FIG. 1

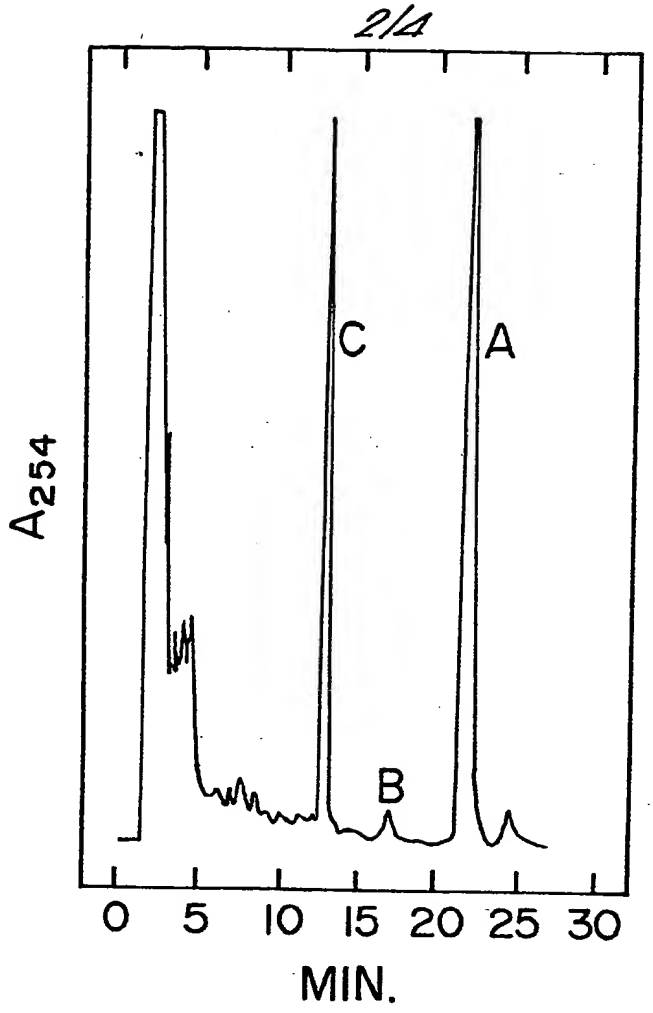
2/4
A254
C
A
B
0 5 10 15 20 25 30
MIN.

FIG. 2

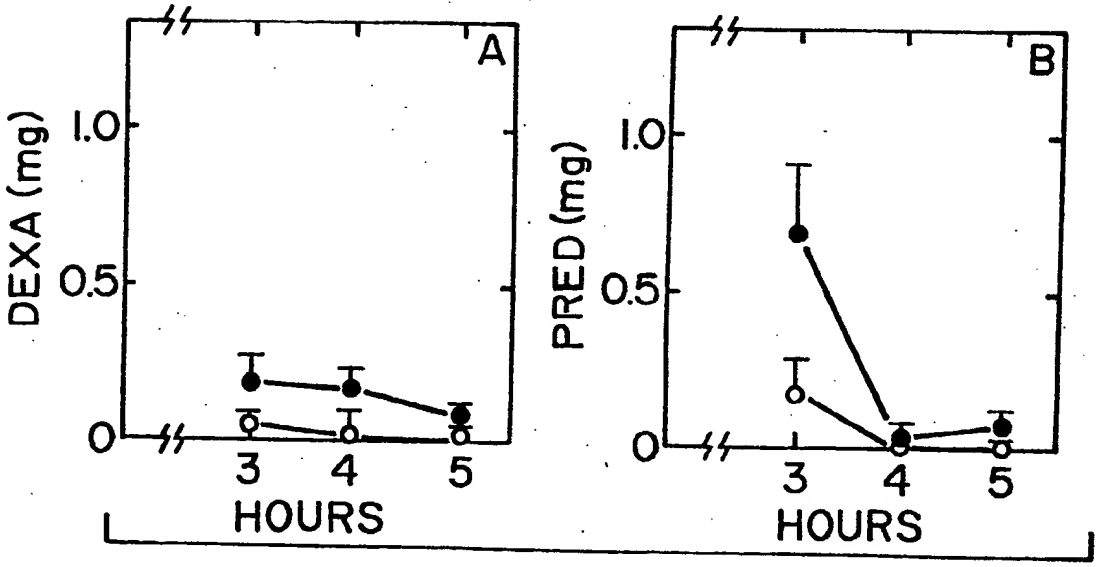
A
DEXA (mg)
1.0
0.5
0
3 4 5
HOURS
B
PRED (mg)
1.0
0.5
0
3 4 5
HOURS

FIG. 4

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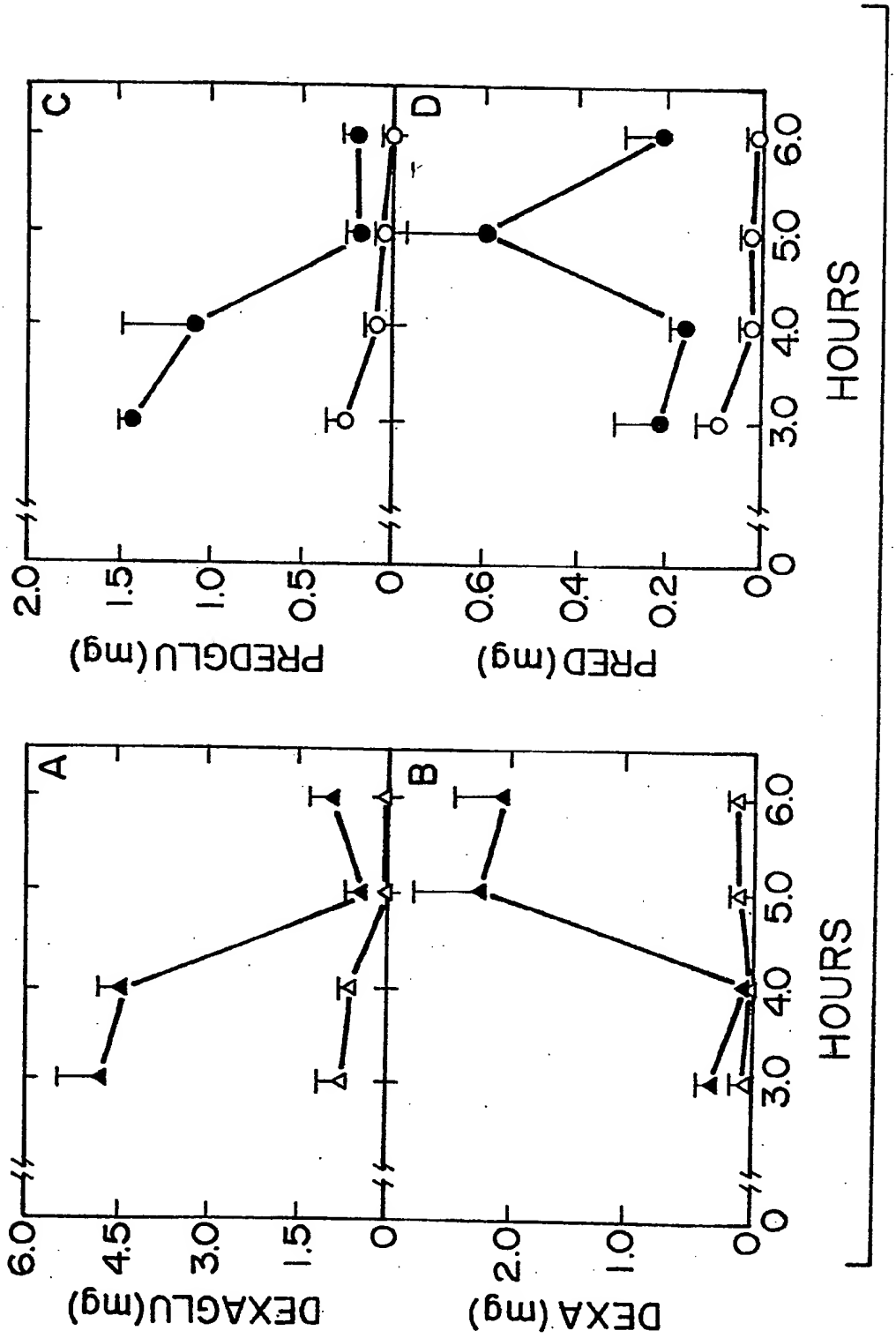
A
B
C
D
DEXAGLU(mg)
DEXA (mg)
PREDGLU(mg)
PRED (mg)
HOURS
HOURS
6.0
4.5
3.0
1.5
0
2.0
1.0
0
2.0
1.5
1.0
0.5
0
0.6
0.4
0.2
0
3.0
4.0
5.0
6.0

FIG. 3

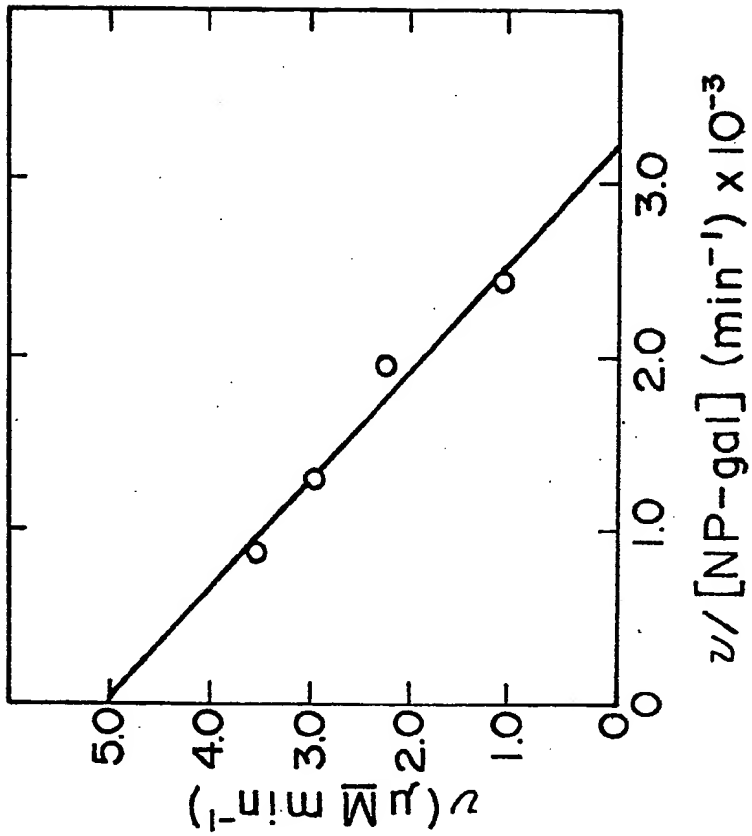
v (μM min⁻¹)
v/[NP-gal] (min⁻¹) x 10⁻³
0
1.0
2.0
3.0
4.0
5.0

FIG. 6

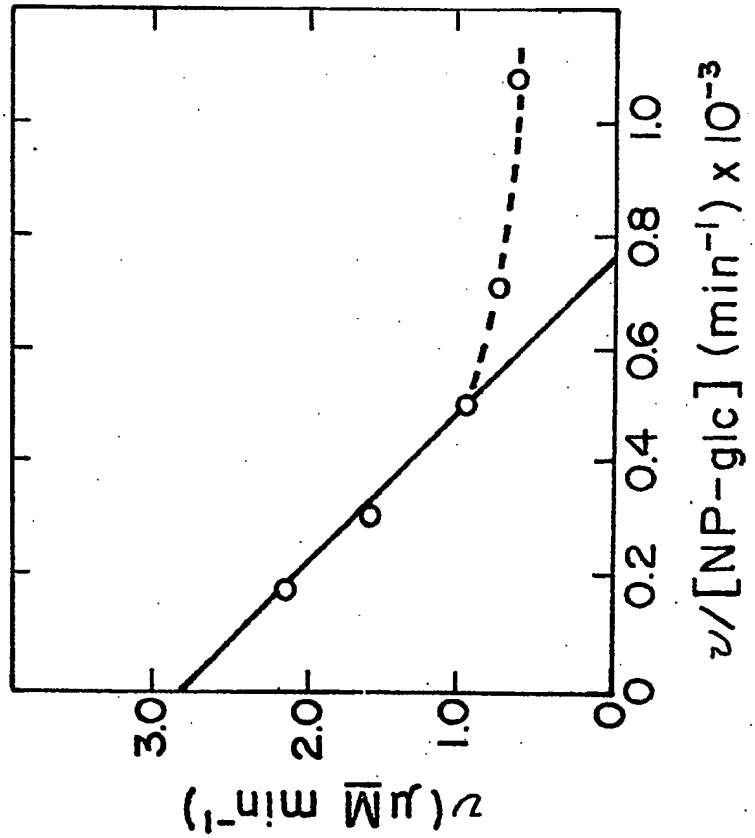
v (μM min⁻¹)
v/[NP-glc] (min⁻¹) x 10⁻³
0
0.2
0.4
0.6
0.8
1.0
2.0
3.0

FIG. 5

(19) JAPANESE PATENT OFFICE

PATENT ABSTRACTS OF JAPAN

(11) Publication number: **08253413 A**

(43) Date of publication of application: **01.10.96**

(51) Int. Cl **A61K 9/48**

(21) Application number: **08042630**

(22) Date of filing: **29.02.96**

(30) Priority: **01.03.95 US 95 396715**

(71) Applicant: **TAKADA KANJI**

(72) Inventor: **TAKADA KANJI**

(54) SLOW-RELEASING ORAL PREPARATION OF LOW-MOLECULAR MEDICINE

(57) Abstract:

PURPOSE: To obtain a pharmaceutical preparation which comprises a water-insoluble macromolecular membrane containing a water-soluble medicine and a gel-forming material and can control its sustained release of the medicine by controlling the number and size of the fine pores in the membrane and the kind and amount of the gelforming material.

CONSTITUTION: In this sustained release preparation, the water-soluble and low- molecular-weight medicine and the gel-forming material are contained in the spaces surrounded by a water-insoluble macromolecular membrane having fine pores and the sustained release of the medicine is controlled by specifying the number and size of the fine pores in the water-insoluble membrane and selecting the kind and amount of the gel-forming material. The gel-forming material is suitably a polyacrylic acid polymer, particularly a carboxy-vinyl polymer. This preparation is particularly produced by allowing a matrix comprising a water-insoluble macromolecular material such as ethyl cellulose and a water-insoluble low-molecular-weight material such as stearic acid to include an ionic and chelate low-molecular-weight medicine and can release the medicinal ingredient substantially in the zero-order reaction, whiel the initial burst is being suppressed. The content of the medicine is 0.1-50% in this preparation.

(19) JAPANESE PATENT OFFICE

PATENT ABSTRACTS OF JAPAN

(11) Publication number: **06192107 A**

(43) Date of publication of application: **12.07.94**

(51) Int. Cl **A61K 31/70**
A61K 47/12
A61K 47/14
A61K 47/44
// C07H 15/256

(21) Application number: **04347158**

(22) Date of filing: **25.12.92**

(71) Applicant: **SANWA KAGAKU KENKYUSHO CO LTD**

(72) Inventor: **SATO MAKOTO**
YOSHINA SHIGEAKI
SATO YUJI
AWATANI JUICHI
HIRAIDE KINYA
SAWAI KIICHI

(54) GLYCYRRHIZIN ORAL AGENT

(57) Abstract:

PURPOSE: To obtain a glycyrrhizin oral agent excellent in absorption from the upper part of the small intestine.

CONSTITUTION: This oral agent is obtained by converting a principal medicine selected from glycyrrhetinic acid and salts thereof into a fat emulsion or a complex lipid mixture, blending an absorbefacient, etc., therewith, providing dried powder, further forming the resultant powder according to a conventional method and coating the formed powder with an enteric film.

(19) JAPANESE PATENT OFFICE

PATENT ABSTRACTS OF JAPAN

(11) Publication number: **09087169 A**

(43) Date of publication of application: **31.03.97**

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A61K 45/00
A61K 47/04
A61K 47/12
A61K 47/32
A61K 47/38

(21) Application number: **08187952**

(22) Date of filing: **18.07.96**

(30) Priority: **20.07.95 JP 07183655**

(71) Applicant: **TANABE SEIYAKU CO LTD**

(72) Inventor: **HATANO HARUMI**
ITO TAKAHIRO
ISHIBASHI TAKASHI
YOSHINO KOUSUKE
MIZOBE MASAKAZU

(54) **COATED CAPSULE PREPARATION OF DIGESTIVE TRACT LOWER PART RELEASE TYPE**

(57) Abstract:

PROBLEM TO BE SOLVED: To obtain a capsule reparation comprising a hard capsule containing an acidic substance, a membrane soluble at a low pH covering the hard capsule and an enteric membrane covering the membrane, capable of rapidly releasing the inner content of the hard capsule to an arbitrary site such as large intestine at the lower part of a digestive tract, etc.

SOLUTION: This coated capsule preparation of digestive tract lower part release type comprises a hard capsule containing at least an acidic substance such as an organic acid, an inorganic acid, etc., as a solid substance showing 2pH 5 after being dissolved in water, a membrane such as a polyvinyl acetal diethyl aminoacetate, etc., soluble at a low pH covering the hard capsule and an enteric membrane such as hydroxypropylmethyl cellulose acetate succinate covering the membrane.

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(19) JAPANESE PATENT OFFICE

PATENT ABSTRACTS OF JAPAN

(11) Publication number: **10226650 A**

(43) Date of publication of application: **25.08.98**

(51) Int. Cl **A61K 31/70**
A61K 47/12

(21) Application number: **09049824**

(22) Date of filing: **18.02.97**

(71) Applicant: **ONO PHARMACEUT CO LTD**

(72) Inventor: **YAMAMOTO MASANOBU**
KIN JUNJI
TERAJIMA HIROSHI

(54) **GLYCYRRHIZIN ORAL PREPARATION**

(57) Abstract:

PROBLEM TO BE SOLVED: To obtain a glycyrrhizin oral preparation capable of importing glycyrrhizin in the oral preparation to blood without degradation in digestive tract by allowing the release of the glycyrrhizin or a salt thereof and an absorption promoter from the oral preparation to be carried out in a dissolved state at the bottom of the digestive tract.

SOLUTION: This glycyrrhizin oral preparation is the one obtained by coating glycyrrhizins as a principal ingredient, and an absorption promoter with an enteric coating material. The absorption promoter is a middle chain fatty acid, e.g. capric acid or an alkali metal salt thereof, especially capric acid or sodium caprate, and polyethylene glycol, propylene glycol, distilled water, etc., are used as a solubilizing agent. The formulating mol ratio of the glycyrrhizins as the principal ingredient to the absorption promoter is (20:1) to (1:20), and the preferable preparation comprises 5-30wt.% glycyrrhizin, 5-30wt.% capric acid or the salt thereof, 20-50wt.% polyethylene glycol, 0-10wt.% propylene glycol, 0-10wt.% distilled water and 0-3wt.% caustic soda to provide 100wt.%. The enteric coating material is carboxymethyl ethyl cellulose, an azo polymer, etc.

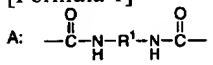
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention relates to the oral tablet which raised the translatability to the inside of glycyrrhizin and the blood of the salt.
[0002]
[Description of the Prior Art] Glycyrrhizin and its derivative, or those salts are independent, or it is blended with amino acid etc., and having various kinds of medicinal action, for example, an anti-cortisone operation, a decholesterolization operation, an anti-allergy operation, anti-inflammatory activity, a detoxifying effect, a gastric ulcer restoration operation, etc. is known. Moreover, recently, a glycyrrhizin tablet is used in many cases as the tablet for liver disease treatment, especially injection by having reported the usefulness of the extensive medication by the intravenous injection of the glycyrrhizin to chronic liver disease, or its salt (it may abbreviate to glycyrrhizin hereafter). However, since it was generally needed for liver disease to pitch in successive games a medicine over a long period of time comparatively, in order that the medication method by the intravenous injection of a glycyrrhizin tablet not only gives sharp pain, but medication might cross it to a patient at every day and a long period of time at the time of medication, it also had the problem of making the organization of an injection site producing thickening.
[0003] Then, although it becomes the best method of solving these troubles to consider glycyrrhizin as an oral tablet, it is reported that the guru chill RICHIN oral tablet of the systemic-action expectation marketed now has a problem in the translatability to the inside of blood for the metabolism by the first time passage effect in the decomposition and liver by the enzyme within an alimentary canal etc. Moreover, the guru chill RICHIN oral tablet marketed now -- the decomposition product produced with the enzyme within an alimentary canal etc. has possibility of causing side effects, such as fake aldosteronism -- includes the remarkable trouble.
[0004] Therefore, many examination of tablet-izing made to shift into blood is performed without decomposition of glycyrrhizin within an alimentary canal by methods other than vein medication. For example, about the suppository, the following are reported as dosage forms replaced with a glycyrrhizin oral tablet.
(1) If rectum medication of guru chill RICHIN is carried out, since it will be absorbed from the rectum and will shift into blood, the possibility of a suppository is reported (refer to JP,3-2122,A).
(2) It is reported by the method of distributing glycyrrhizin to the bases (for example, Witepsol, migriol, etc.) of lipophilic property, and carrying out rectum medication that shift into the blood of glycyrrhizin is promoted (refer to JP,3-123731,A).
(3) It is reported by by blending at least one of non-ion system surfactants (for example, polyoxyethylene lauryl ether etc.) and the medium-chain-fatty-acid salts (alkali-metal salt of the fatty acid of the inside chain of a capric acid or a caproic acid) with glycyrrhizin as an absorption accelerator that the suppository which shows the outstanding absorptivity is obtained (refer to JP,4-261117,A).
[0005] (4) It is reported by nonionic surfactants (for example, polyoxyethylene alkyl ether etc.) and by blending water-soluble carboxylic acids (a capric acid, malonic acid, etc.) and the salt of those if needed further as glycyrrhizin and an absorption accelerator that the suppository which shows the outstanding absorptivity is obtained (refer to JP,5-97680,A).
(5) It is reported by by blending absorption accelerators (for example, capric-acid sodium etc.), pH regulator (for example, sodium hydroxide), or a URUSODESOKI sea-coal acid with glycyrrhizin that the suppository which shows the outstanding absorptivity is obtained (refer to JP,7-82155,A).
[0006] However, there are many patients to whom the prolonged administration of a suppository also complains of the dissatisfaction even if it is not comparable to the injection, and an oral tablet is too desired in prolonged administration. Then, examination of the following tablet-izing is reported about considering glycyrrhizin as an oral tablet.
(6) It is reported that the oral tablet which blends glycyrrhizin and a fatty-acid glyceride (for example, the monochrome, JI, or the triglyceride of a fatty acid of the inside chain of stearin acid or a caprylic acid), covers with an enteric nature coat, tablet-izes, and shows the outstanding absorptivity is obtained (refer to JP,3-255037,A).
[0007] (7) glycyrrhizin -- a fat emulsion or a conjugated lipid -- consider as a mixture, blend an absorption accelerator (a non-ion system surfactant, medium chain fatty acid (for example, capric acid), its salts, and its glyceride) etc., and consider as dryness powder Furthermore, it fabricates, and it covers with an enteric nature coat, and tablet-izes, and it is reported that the oral tablet which shows the absorptivity which was excellent in the small intestine upper part is obtained (refer to JP,6-192107,A). However, these tablets do not show sufficient absorption to the inside of the body still more compared with

the blood drug concentration of the injection which the effect has decided.
[0008]
[Means for Solving the Problem] As a result of examining wholeheartedly the tablet method of improving the absorptivity to the inside of the body in the internal use of glycyrrhizin, this invention persons Then, glycyrrhizin or its salt, At least one of medium chain fatty acid and the salts of its is made to contain as an absorption accelerator, a pH regulator is added if needed, it solubilizes by the solubilizing agent, this is further covered with an enteric nature coat, and an oral tablet is formed, That is, it found out that the absorptivity which was extremely superior to the conventional oral tablet was shown by performing discharge from the tablet of a chief remedy and an absorption accelerator in the alimentary canal lower part (especially large intestine) in the state where it solubilized.
[0009] Generally, it is reported that the medium chain fatty acid as an absorption accelerator and the absorption facilitatory effect of the salts have the largest large intestine in an alimentary canal (development "the medicine sending method" of a drug, 13, 50 -73 (1988) reference), and the method of sending a medicine to the large intestine has been developed (refer to JP,3-7718,A). However, since the large intestine is a part which absorbs moisture, moisture is not fully supplied like the alimentary canal upper part, but it has very little moisture within the normal large intestine. Therefore, the improvement of sufficient absorption was not accepted only by sending a solid medicine and a solid absorption accelerator simply to the large intestine. Then, the solubilizing agent of this invention solves this trouble by solubilizing a solid medicine and a solid absorption accelerator.
[0010] solubilizing medium chain fatty acid and its salts as glycyrrhizin and an absorption accelerator -- the conventional technology (7) -- a fat emulsion or a conjugated lipid -- it is thought that it was very difficult as it understands, even if it sees from considering as the mixture However, this invention persons succeeded in solubilizing by using the solubilizing agent of this invention. That is, solubilizing and forming the medium chain fatty acid and its salts as glycyrrhizin and its salt, and an absorption accelerator into an oral tablet by the solubilizing agent of this invention is finished for the first time by this invention persons.
[0011]
[Elements of the Invention] this invention solubilizes at least one sort of chief remedies and the absorption accelerator which are chosen from (1) glycyrrhizin and its salt by the solubilizing agent. The glycyrrhizin internal use tablet characterized by covering with an enteric nature coat, (2) It is related with the internal use tablet of the aforementioned (1) publication characterized by making at least one of medium chain fatty acid and the salts of its contain as an absorption accelerator, and the internal use tablet of the aforementioned (2) publication whose (3) absorption accelerators are a capric acid and/or its sodium salt.
[0012] As a salt of the glycyrrhizin of the chief remedy in this invention tablet what is permitted as physic -- it is -- ****ing -- alkali metal (a potassium --) Salts, such as sodium, the salt of alkaline earth metal (calcium, magnesium, etc.), an ammonium salt and the organic amine (tetramethylammonium --) permitted pharmacologically A triethylamine, a monomethylamine, a dimethylamine, a cyclopentyl amine, Salts, such as a benzylamine, phenethylamine, a piperidine, a monoethanolamine, a diethanolamine, a tris (hydroxymethyl) aminomethane, a lysine, an arginine, and an N-methyl-D-glucamine, etc. are mentioned. A glycyrrhizin disodium salt, glycyrrhizin and 2 potassium salt, or a glycyrrhizin monochrome ammonium salt is especially desirable. These are independent, or can use together and use two kinds.
[0013] As the medium chain fatty acid of the absorption accelerator in this invention tablet, and its salts, the salt of those alkali metal (a potassium, sodium, etc.), such as a capric acid, a caprylic acid, and a caproic acid, the salt of alkaline earth metal (calcium, magnesium, etc.), etc. are mentioned, for example. Also in these, especially a capric acid or capric-acid sodium salt is desirable.
[0014] as a solubilizing agent in this invention tablet, a polyethylene glycol, for example, [polyethylene-glycol 400(registered trademark, following, PEG400)], propylene-glycol, and nonionic-surfactant [(HCO-60), for example, hydrogenation hardening castor oil,], distilled water, etc. are mentioned, and these are independent -- or it can be combined and used Especially as a solubilizing agent, the combination of PEG400, a propylene glycol, and distilled water or the combination of PEG400 and distilled water is desirable.
[0015] Although the compounding ratio with the glycyrrhizin of a chief remedy and an absorption accelerator changes with kinds of absorption accelerator, they are 20:1 - 1:20 as a mole ratio, and are 8:1-1:8 more preferably.
[0016] When combining desirable PEG400 and a desirable propylene glycol, and distilled water especially as a solubilizing agent, those compounding ratios are 6:1:1-1:1:1 as a weight ratio, and are 4:1:1-3:1:1 more preferably. Moreover, the compounding ratios in the case of combining PEG400 and distilled water are 6:1-1:1 as a weight ratio, and are 4:1-3:1 more preferably.
[0017] The compounding ratio of the capric acid as the glycyrrhizin and the absorption accelerator of a chief remedy, and the sodium hydroxide as the salt, PEG400 as a solubilizing agent, propylene glycol, distilled water, and pH regulator The capric acid and its salt as an absorption accelerator five to 30% of the weight 5 - 30 % of the weight, [the glycyrrhizin of a chief remedy, and its salt] 0 - 3% of the weight of composition is [a propylene glycol / distilled water / a sodium hydroxide] desirable [PEG400 / zero to 10% of the weight] zero to 10% of the weight 20 to 50% of the weight (however, the sum total of all combination is 100 % of the weight.). .
[0018] As a pH regulator in this invention tablet, the hydrate of alkali metal (a potassium, sodium, etc.) or the hydrate of alkaline earth metal (calcium, magnesium, etc.) is desirable. Especially, a sodium hydroxide is desirable.
[0019] Carboxy methyl ethyl cellulose, hydroxypropyl-methylcellulose phthalate, a cellulose acetate, a methacrylic-acid

system copolymer, azo polymer, etc. can be used that what is necessary is just what is usually used for a medicine as a material of the enteric nature coat in this invention tablet. What could use what is generally known as azo polymer, for example, was indicated by JP,3-7718,A is mentioned. Preferably, it is JP,3-7718,A and they are the following formulas A, B, C, and D [0020].

[Formula 1]

A: 

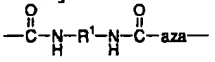
B: —aza—

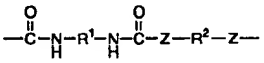
C: Z—R^2—Z

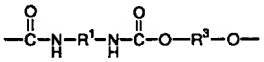
D: —O—R^3—O—

A-B, A-C, and A-D [0021] out of which it comes and which are produced with the combination of a structural unit shown

[Formula 2]

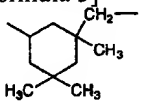
A-B: 

A-C: 

A-D: 

Azo polymer which it has ********** as a segment and A-B, A-C, and segment mole-ratio x:y:z of A-D become from two or more segments whose average molecular weight is 1000-100000 in 0.01-0.8:0-0.80:0-0.99 (however, it is x+y+z=1.0) [0022] The inside of [formula and R1 are a formula (1).

[Formula 3]

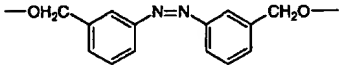


(1)

It comes out, the basis shown is expressed, three R1 in each segment of A-B, A-C, and A-D expresses the same machine, and aza is a formula (2).

[0023]

[Formula 4]



(2)

It comes out, the basis shown is expressed, Z-R2-Z expresses the residue of a polyethylene glycol, and R3 expresses 1 and 2-propylene.] Azo polymer given in the examples 12 and 12 of JP,3-7718,A (a) is still more desirable.

[0024] As dosage forms of the oral tablet of this invention, a capsule is desirable and a soft capsule is still more desirable. You may make a stabilizer, a surfactant, a diluent, an additive, lubricant, a solubilizing agent, and antiseptics contain on the occasion of tablet-izing if needed. Although there is especially no limit and it changes with a symptom, age, etc. if the glycyrrhizin content in this invention is an amount which can discover the effect of a medicine, preferably, single dose is 1-500mg, and can prescribe a medicine for the patient 1 to several times per day.

[0025]

[Effect] By making at least one of medium chain fatty acid and the salts of its contain as glycyrrhizin or its salt, and an absorption accelerator, solubilizing by the solubilizing agent, covering this with an enteric nature coat and forming it into an oral tablet further, a medicine will send the alimentary canal lower part (especially large intestine) by internal use, and it becomes possible to make the inside of the body absorb glycyrrhizin or its salt by high concentration. Moreover, the extensive medication from which sufficient pharmacology effect which is equal to vein medication is acquired becomes possible by internal use.

[0026]

[Example] Hereafter, although this invention is explained in full detail by the example of manufacture, and the example of an experiment, this invention is not limited to these. The section means the weight section among the following examples.

[0027] The example 1 of manufacture: The polyethylene glycol 400 and the propylene glycol were mixed by component combination of the solution prescription following, and it added gradually, ****(ing) a glycyrrhizin ammonium salt. Churning mixture was carried out and the solution was prepared until it added a capric acid and sodium salt powder to the obtained solution and became clear.

[0028]

[Table 1]

** A part Loadings A glycyrrhizin ammonium salt The 30 sections A capric acid and sodium salt The 12 sections propylene glycol The five sections Polyethylene glycol 400 The 53 sections A total of 100 sections [0029] The example 2 of

manufacture: The polyethylene glycol 400 and the propylene glycol were mixed with the component loadings of the solution prescription following, and it added gradually, ****(ing) glycyrrhizin and 2 potassium salt. Churning mixture was carried out and the solution was prepared until it added a capric acid and sodium salt powder to the obtained solution and became clear.
[0030]
[Table 2]
** A part Loadings Glycyrrhizin and 2 potassium salt The 30 sections A capric acid and sodium salt The 12 sections propylene glycol The five sections Polyethylene glycol 400 The 53 sections A total of 100 sections [0031] The example 3 of manufacture: The polyethylene glycol 400 and the propylene glycol were mixed with the component loadings of the solution prescription following, and it added gradually, ****(ing) a glycyrrhizin disodium salt. The capric acid which carried out melting to the obtained solution was added, churning mixture was carried out, and the solution was prepared.
[0032]
[Table 3]
** A part Loadings A glycyrrhizin disodium salt The 30 sections A capric acid The 12 sections Propylene glycol The ten sections Polyethylene glycol 400 The 48 sections A total of 100 sections [0033] The example 4 of manufacture: The polyethylene glycol 400 was mixed in the solution which dissolved the sodium hydroxide in water with the component loadings of the solution prescription following, and it added gradually, ****(ing) a glycyrrhizin ammonium salt. The capric acid which carried out melting to the obtained solution was added, churning mixture was carried out, and the solution was prepared.
[0034]
[Table 4]
** A part Loadings A glycyrrhizin ammonium salt The 30 sections A capric acid The 15 sections Water The 8.8 sections Sodium hydroxide The 1.2 sections Polyethylene glycol 400 45 **** The 100 sections [0035] The example 5 of manufacture: The polyethylene glycol 400 was mixed in the solution which dissolved the sodium hydroxide in water with the component loadings of the solution prescription following, and it added gradually, ****(ing) a glycyrrhizin ammonium salt. The capric acid which carried out melting to the obtained solution was added, churning mixture was carried out, and the solution was prepared.
[0036]
[Table 5]
** A part Loadings A glycyrrhizin ammonium salt The 20 sections A capric acid The 25 sections Water The 8.3 sections Sodium hydroxide The 1.7 sections Polyethylene glycol 400 45 **** The 100 sections [0037] The example 6 of manufacture: The polyethylene glycol 400 was mixed in the solution which dissolved the sodium hydroxide in water with the component loadings of the solution prescription following, and it added gradually, ****(ing) a glycyrrhizin ammonium salt. The capric acid which carried out melting to the obtained solution was added, churning mixture was carried out, and the solution was prepared.
[0038]
[Table 6]
** A part Loadings A glycyrrhizin ammonium salt The 15 sections A capric acid The 30 sections Water The 7.7 sections Sodium hydroxide The 2.3 sections Polyethylene glycol 400 45 **** The 100 sections [0039] The example 7-1 of manufacture: The soft capsule which contains about 45mg per capsule of glycyrrhizin disodium salts for what was manufactured in the example 1 of oral tablet manufacture of solution prescription per capsule according to a conventional method was **(ed), and it considered as the oral tablet.
[0040] The example 7-2 to 7-6 of manufacture: Although manufactured in the example 1 of oral tablet manufacture of solution prescription, by carrying out the same operation as the example 7-1 of manufacture using what was instead manufactured in the examples 2-6 of manufacture, it considered as the oral tablet.
[0041] The example 8-1 of manufacture: Using the spray pan-coating machine, according to the conventional method, carboxy methyl ethyl cellulose was coated 10%, and the soft capsule which manufactured solution prescription in the example 7-1 of oral tablet manufacture coated with the enteric nature coat was considered as the oral tablet.
[0042] The example 8-2 to 8-6 of manufacture: Although solution prescription was manufactured in the example 7-1 of oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 8-1 of manufacture using what was instead manufactured in the example 7-2 to 7-6 of manufacture, it considered as the oral tablet.
[0043] The example 9-1 of manufacture: Using the spray pan-coating machine, according to the conventional method, carboxy methyl ethyl cellulose was coated 15%, and the soft capsule which manufactured solution prescription in the example 7-1 of oral tablet manufacture coated with the enteric nature coat was considered as the oral tablet.
[0044] The example 9-2 to 9-6 of manufacture: Although solution prescription was manufactured in the example 7-1 of oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 8-1 of manufacture using what was instead manufactured in the example 7-2 to 7-6 of manufacture, it considered as the oral tablet.
[0045] The example 10-1 of manufacture: According to the conventional method, azo polymer (example 12 of JP,3-7718,A) was coated 5% using the spray pan-coating machine, and the tablet which manufactured solution prescription in the example 8-1 of oral tablet manufacture coated with the enteric nature coat was considered as the oral tablet.
[0046] The example 10-2 to 10-6 of manufacture: Although solution prescription was manufactured in the example 8-1 of oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 10-1 of manufacture

using what was instead manufactured in the example 8-2 to 8-6 of manufacture, it considered as the oral tablet.
[0047] The example 1 of comparison: Using non PARERU (refined-sugar particle, 24 - 34 meshes) 500g as an oral tablet nucleus of powder prescription, with the centrifugal fluidized-bed-granulation machine which corns the following powder, by the conventional method, granulatio with a diameter of about 1mm was **(ed) and it considered as the oral tablet. Finally, the glycyrrhizin disodium salt became 39.4% among [all] the tablet, and a capric acid and sodium salt became about 17%.
[0048]
[Table 7]
** A part Loadings A glycyrrhizin disodium salt The 53 sections A capric acid and sodium salt The 25 sections Hydroxypropylcellulose (L-HPC) The 15 sections Microcrystal nature cellulose (Avicel) The seven sections A total of 100 sections [0049] The example 2 of comparison: The tablet which manufactured powder prescription in the example 1 of oral tablet comparison coated with the enteric nature coat was coated with 10% and azo polymer (example 12 of JP,3-7718,A) 7% with carboxy methyl ethyl cellulose according to the conventional method using the spray pan-coating machine, and was considered as the oral tablet.
[0050] Internal use was carried out to the beagle which abstained from food overnight [example of experiment 1] by kg in 50mg /by having used ****** of the example 7-1 of manufacture, 8-1, 9-1, 10-1, the example 1 of comparison, and the example 2 of comparison as the glycyrrhizin disodium salt, and it administered intravenously by kg in 2mg /, and collected blood from the forearm vein with time, and plasma was obtained by the conventional method. The concentration of the glycyrrhizin in this plasma was measured by the high performance chromatography, and it asked for the curvilinear undersurface product (AUC and mg-min/ml) from 0 hour to [from the obtained concentration in plasma] 8 hours. The utilization factor was computed by comparison with intravenous administration. The result is shown in Table 1. Moreover, internal use of the glycyrrhizin oral tablet (100mg/(kg)) marketed the example 10-1 (50mg/(kg)) of manufacture and now is carried out to a beagle (3-6 animals), and the result which investigated concentration (average ** deflection) transition of the glycyrrhizin in plasma with time is shown in drawing 1 .
[0051]
[Table 8]
Table 1 Medication part The amount of medication AUC (mg-min/ml) Utilization factor Solution A vein 2mg/kg 3408. 0 100% A commercial lock Taking orally 100mg/kg 310.2 0.2% The example 1 of comparison Taking orally 50mg/kg 653.4 0.8% Example of comparison 2 taking orally 50mg/kg 1202. 0 1.4% The example 7-1 of manufacture Taking orally 50mg/kg 2010. 0 2.4% Example 8-1 of manufacture Taking orally 50mg/kg 3378.0 4.0% Example 9-1 of manufacture Taking orally 50mg/kg 4656.2 Example 10-1 of 5.5% manufacture Taking orally 50mg/kg 5140.5 6.0% [0052] Consideration: The tablet of this invention showed the absorptivity which was extremely superior to the above-mentioned result compared with the oral tablet (example 2 of comparison) which coated a commercial oral tablet, the oral tablet (example 1 of comparison) of powder prescription, and powder prescription with the enteric nature coat. This enabled it to improve the absorptivity to the inside of the body in the internal use of glycyrrhizin and its salt.

[Translation done.]

TECHNICAL FIELD

[The technical field to which invention belongs] this invention relates to the oral tablet which raised the translatability to the inside of glycyrrhizin and the blood of the salt.

[Translation done.]

* NOTICES *

EFFECT OF THE INVENTION

[Effect] By making at least one of medium chain fatty acid and the salts of its contain as glycyrrhizin or its salt, and an absorption accelerator, solubilizing by the solubilizing agent, covering this with an enteric nature coat and forming it into an oral tablet further, a medicine will send the alimentary canal lower part (especially large intestine) by internal use, and it becomes possible to make the inside of the body absorb glycyrrhizin or its salt by high concentration. Moreover, the extensive medication from which sufficient pharmacology effect which is equal to vein medication is acquired becomes possible by internal use.

[Translation done.]

TECHNICAL PROBLEM

[Description of the Prior Art] Glycyrrhizin and its derivative, or those salts are independent, or it is blended with amino acid etc., and having various kinds of medicinal action, for example, an anti-cortisone operation, a ** cholesterol operation, an anti-allergy operation, anti-inflammatory activity, a detoxifying effect, a gastric ulcer restoration operation, etc. is known. Moreover, recently, a glycyrrhizin tablet is used in many cases as the tablet for liver disease treatment, especially injection by having reported the usefulness of the extensive medication by the intravenous injection of the glycyrrhizin to chronic liver disease, or its salt (it may abbreviate to glycyrrhizin hereafter). However, since it was generally needed for liver disease to pitch in successive games a medicine over a long period of time comparatively, in order that the medication method by the intravenous injection of a glycyrrhizin tablet not only gives sharp pain, but medication might cross it to a patient at every day and a long period of time at the time of medication, it also had the problem of making the organization of an injection site producing thickening.

[0003] Then, although it becomes the best method of solving these troubles to consider glycyrrhizin as an oral tablet, it is reported that the guru chill RICHIN oral tablet of the systemic-action expectation marketed now has a problem in the translatability to the inside of blood for the metabolism by the first time passage effect in the decomposition and liver by the enzyme within an alimentary canal etc. Moreover, the guru chill RICHIN oral tablet marketed now -- the decomposition product produced with the enzyme within an alimentary canal etc. has possibility of causing side effects, such as fake aldosteronism -- includes the remarkable trouble.

[0004] Therefore, many examination of tablet-izing made to shift into blood is performed without decomposition of glycyrrhizin within an alimentary canal by methods other than vein medication. For example, about the suppository, the following are reported as dosage forms replaced with a glycyrrhizin oral tablet.

(1) If rectum medication of guru chill RICHIN is carried out, since it will be absorbed from the rectum and will shift into blood, the possibility of a suppository is reported (refer to JP,3-2122,A).

(2) It is reported by the method of distributing glycyrrhizin to the bases (for example, Witepsol, migriol, etc.) of lipophilic property, and carrying out rectum medication that shift into the blood of glycyrrhizin is promoted (refer to JP,3-123731,A).

(3) It is reported by by blending at least one of non-ion system surfactants (for example, polyoxyethylene lauryl ether etc.) and the medium-chain-fatty-acid salts (alkali-metal salt of the fatty acid of the inside chain of a capric acid or a caproic acid) with glycyrrhizin as an absorption accelerator that the suppository which shows the outstanding absorptivity is obtained (refer to JP,4-261117,A).

[0005] (4) It is reported by nonionic surfactants (for example, polyoxyethylene alkyl ether etc.) and by blending water-soluble carboxylic acids (a capric acid, malonic acid, etc.) and the salt of those if needed further as glycyrrhizin and an absorption accelerator that the suppository which shows the outstanding absorptivity is obtained (refer to JP,5-97680,A).

(5) It is reported by by blending absorption accelerators (for example, capric-acid sodium etc.), pH regulator (for example, sodium hydroxide), or a URUSODESOKI sea-coal acid with glycyrrhizin that the suppository which shows the outstanding absorptivity is obtained (refer to JP,7-82155,A).

[0006] However, there are many patients to whom the prolonged administration of a suppository also complains of the dissatisfaction even if it is not comparable to the injection, and an oral tablet is too desired in prolonged administration. Then, examination of the following tablet-izing is reported about considering glycyrrhizin as an oral tablet.

(6) It is reported that the oral tablet which blends glycyrrhizin and a fatty-acid glyceride (for example, the monochrome, JI, or the triglyceride of a fatty acid of the inside chain of stearin acid or a caprylic acid), covers with an enteric nature coat, tablet-izes, and shows the outstanding absorptivity is obtained (refer to JP,3-255037,A).

[0007] (7) glycyrrhizin -- a fat emulsion or a conjugated lipid -- consider as a mixture, blend an absorption accelerator (a non-ion system surfactant, medium chain fatty acid (for example, capric acid), its salts, and its glyceride) etc., and consider as dryness powder Furthermore, it fabricates, and it covers with an enteric nature coat, and tablet-izes, and it is reported that the oral tablet which shows the absorptivity which was excellent in the small intestine upper part is obtained (refer to JP,6-192107,A). However, these tablets do not show sufficient absorption to the inside of the body still more compared with the blood drug concentration of the injection which the effect has decided.

[Translation done.]

MEANS

[Means for Solving the Problem] As a result of examining wholeheartedly the tablet method of improving the absorptivity to the inside of the body in the internal use of glycyrrhizin, this invention persons Then, glycyrrhizin or its salt, At least one of medium chain fatty acid and the salts of its is made to contain as an absorption accelerator, a pH regulator is added if needed, it solubilizes by the solubilizing agent, this is further covered with an enteric nature coat, and an oral tablet is formed, That is, it found out that the absorptivity which was extremely superior to the conventional oral tablet was shown by performing discharge from the tablet of a chief remedy and an absorption accelerator in the alimentary canal lower part (especially large intestine) in the state where it solubilized.

[0009] Generally, it is reported that the medium chain fatty acid as an absorption accelerator and the absorption facilitatory effect of the salts have the largest large intestine in an alimentary canal (development "the medicine sending method" of medical supplies, 13, 50 -73 (1988) reference), and the method of sending a medicine to the large intestine has been developed (refer to JP,3-7718,A). However, since the large intestine is a part which absorbs moisture, moisture is not fully supplied like the alimentary canal upper part, but it has very little moisture within the normal large intestine. Therefore, the improvement of sufficient absorption was not accepted only by sending a solid medicine and a solid absorption accelerator simply to the large intestine. Then, the solubilizing agent of this invention solves this trouble by solubilizing a solid medicine and a solid absorption accelerator.

[0010] solubilizing medium chain fatty acid and its salts as glycyrrhizin and an absorption accelerator -- the conventional technology (7) -- a fat emulsion or a conjugated lipid -- it is thought that it was very difficult as it understands, even if it sees from considering as the mixture However, this invention persons succeeded in solubilizing by using the solubilizing agent of this invention. That is, solubilizing and forming the medium chain fatty acid and its salts as glycyrrhizin and its salt, and an absorption accelerator into an oral tablet by the solubilizing agent of this invention is finished for the first time by this invention persons.

[0011]

[Elements of the Invention] this invention solubilizes at least one sort of chief remedies and the absorption accelerator which are chosen from (1) glycyrrhizin and its salt by the solubilizing agent. The glycyrrhizin internal use tablet characterized by covering with an enteric nature coat, (2) It is related with the internal use tablet of the aforementioned (1) publication characterized by making at least one of medium chain fatty acid and the salts of its contain as an absorption accelerator, and the internal use tablet of the aforementioned (2) publication whose (3) absorption accelerators are a capric acid and/or its sodium salt.

[0012] As a salt of the glycyrrhizin of the chief remedy in this invention tablet what is permitted as medicine -- it is -- ****ing -- alkali metal (a potassium --) Salts, such as sodium, the salt of alkaline earth metal (calcium, magnesium, etc.), an ammonium salt and the organic amine (tetramethylammonium --) permitted pharmacologically A triethylamine, a monomethylamine, a dimethylamine, a cyclopentyl amine, Salts, such as a benzylamine, phenethylamine, a piperidine, a monoethanolamine, a diethanolamine, a tris (hydroxymethyl) aminomethane, a lysine, an arginine, and an N-methyl-D-glucamine, etc. are mentioned. A glycyrrhizin disodium salt, glycyrrhizin and 2 potassium salt, or a glycyrrhizin monochrome ammonium salt is especially desirable. These are independent, or can use together and use two kinds.

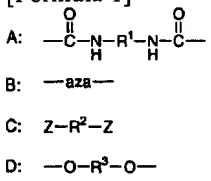
[0013] As the medium chain fatty acid of the absorption accelerator in this invention tablet, and its salts, the salt of those alkali metal (a potassium, sodium, etc.), such as a capric acid, a caprylic acid, and a caproic acid, the salt of alkaline earth metal (calcium, magnesium, etc.), etc. are mentioned, for example. Also in these, especially a capric acid or capric-acid sodium salt is desirable.

[0014] as a solubilizing agent in this invention tablet, a polyethylene glycol, for example, [polyethylene-glycol 400(registered trademark, following, PEG400)], propylene-glycol, and nonionic-surfactant [(HCO-60), for example, hydrogenation hardening castor oil,], distilled water, etc. are mentioned, and these are independent -- or it can be combined and used Especially as a solubilizing agent, the combination of PEG400, a propylene glycol, and distilled water or the combination of PEG400 and distilled water is desirable.

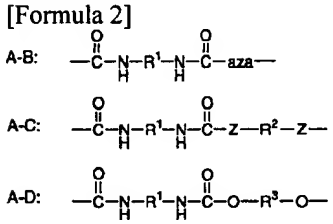
[0015] Although the compounding ratio with the glycyrrhizin of a chief remedy and an absorption accelerator changes with kinds of absorption accelerator, they are 20:1 - 1:20 as a mole ratio, and are 8:1-1:8 more preferably.

[0016] When combining desirable PEG400 and a desirable propylene glycol, and distilled water especially as a solubilizing agent, those compounding ratios are 6:1:1-1:1:1 as a weight ratio, and are 4:1:1-3:1:1 more preferably. Moreover, the compounding ratios in the case of combining PEG400 and distilled water are 6:1-1:1 as a weight ratio, and are 4:1-3:1 more

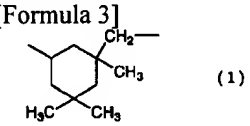
preferably.
[0017] The compounding ratio of the capric acid as the glycyrrhizin and the absorption accelerator of a chief remedy, and the sodium hydroxide as the salt, PEG400 as a solubilizing agent, propylene glycol, distilled water, and pH regulator The capric acid and its salt as an absorption accelerator five to 30% of the weight 5 - 30 % of the weight, [the glycyrrhizin of a chief remedy, and its salt] 0 - 3% of the weight of composition is [a propylene glycol / distilled water / a sodium hydroxide] desirable [PEG400 / zero to 10% of the weight] zero to 10% of the weight 20 to 50% of the weight (however, the sum total of all combination is 100 % of the weight.). .
[0018] As a pH regulator in this invention tablet, the hydrate of alkali metal (a potassium, sodium, etc.) or the hydrate of alkaline earth metal (calcium, magnesium, etc.) is desirable. Especially, a sodium hydroxide is desirable.
[0019] Carboxy methyl ethyl cellulose, hydroxypropyl-methylcellulose phthalate, a cellulose acetate, a methacrylic-acid system copolymer, azo polymer, etc. can be used that what is necessary is just what is usually used for a medicine as a material of the enteric nature coat in this invention tablet. What could use what is generally known as azo polymer, for example, was indicated by JP,3-7718,A is mentioned. Preferably, it is JP,3-7718,A and they are the following formulas A, B, C, and D. [0020]
[Formula 1]



A-B, A-C, and A-D out of which it comes and which are produced with the combination of a structural unit shown. [0021]
[Formula 2]



Azo polymer which it has ********** as a segment and A-B, A-C, and segment mole-ratio x:y:z of A-D become from two or more segments whose average molecular weight is 1000-100000 in 0.01-0.8:0-0.80:0-0.99 (however, it is x+y+z=1.0). [0022] The inside of [formula and R1 are a formula (1).
[Formula 3]



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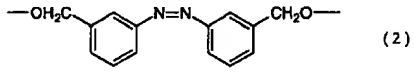

It comes out, the basis shown is expressed, Z-R2-Z expresses the residue of a polyethylene glycol, and R3 expresses 1 and 2-propylene.] Azo polymer given in the examples 12 and 12 of JP,3-7718,A (a) is still more desirable.
[0024] As dosage forms of the oral tablet of this invention, a capsule is desirable and a soft capsule is still more desirable. You may make a stabilizer, a surfactant, a diluent, an additive, lubricant, a solubilizing agent, and antiseptics contain on the occasion of tablet-izing if needed. Although there is especially no limit and it changes with a symptom, age, etc. if the glycyrrhizin content in this invention is an amount which can discover the effect of a medicine, preferably, single dose is 1-500mg, and can prescribe a medicine for the patient 1 to several times per day.

[Translation done.]

EXAMPLE

[Example] Hereafter, although this invention is explained in full detail by the example of manufacture, and the example of an experiment, this invention is not limited to these. The section means the weight section among the following examples.
[0027] The example 1 of manufacture: The polyethylene glycol 400 and the propylene glycol were mixed by component combination of the solution prescription following, and it added gradually, ****(ing) a glycyrrhizin ammonium salt. Churning mixture was carried out and the solution was prepared until it added a capric acid and sodium salt powder to the obtained solution and became clear.
[0028]
[Table 1]
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[0030]
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** A part Loadings Glycyrrhizin and 2 potassium salt The 30 sections A capric acid and sodium salt The 12 sections propylene glycol The five sections Polyethylene glycol 400 The 53 sections A total of 100 sections [0031] The example 3 of manufacture: The polyethylene glycol 400 and the propylene glycol were mixed with the component loadings of the solution prescription following, and it added gradually, ****(ing) a glycyrrhizin disodium salt. The capric acid which carried out melting to the obtained solution was added, churning mixture was carried out, and the solution was prepared.
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[0034]
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[0036]
[Table 5]
** A part Loadings A glycyrrhizin ammonium salt The 20 sections A capric acid The 25 sections Water The 8.3 sections Sodium hydroxide The 1.7 sections Polyethylene glycol 400 45 **** The 100 sections [0037] The example 6 of manufacture: The polyethylene glycol 400 was mixed in the solution which dissolved the sodium hydroxide in water with the component loadings of the solution prescription following, and it added gradually, ****(ing) a glycyrrhizin ammonium salt. The capric acid which carried out melting to the obtained solution was added, churning mixture was carried out, and the solution was prepared.
[0038]
[Table 6]
** A part Loadings A glycyrrhizin ammonium salt The 15 sections A capric acid The 30 sections Water The 7.7 sections Sodium hydroxide The 2.3 sections Polyethylene glycol 400 45 **** The 100 sections [0039] The example 7-1 of manufacture: The soft capsule which contains about 45mg per capsule of glycyrrhizin disodium salts for what was

manufactured in the example 1 of oral tablet manufacture of solution prescription per capsule according to a conventional method was **(ed), and it considered as the oral tablet.
[0040] The example 7-2 to 7-6 of manufacture: Although manufactured in the example 1 of oral tablet manufacture of solution prescription, by carrying out the same operation as the example 7-1 of manufacture using what was instead manufactured in the examples 2-6 of manufacture, it considered as the oral tablet.
[0041] The example 8-1 of manufacture: Using the spray pan-coating machine, according to the conventional method, carboxy methyl ethyl cellulose was coated 10%, and the soft capsule which manufactured solution prescription in the example 7-1 of oral tablet manufacture coated with the enteric nature coat was considered as the oral tablet.
[0042] The example 8-2 to 8-6 of manufacture: Although solution prescription was manufactured in the example 7-1 of oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 8-1 of manufacture using what was instead manufactured in the example 7-2 to 7-6 of manufacture, it considered as the oral tablet.
[0043] The example 9-1 of manufacture: Using the spray pan-coating machine, according to the conventional method, carboxy methyl ethyl cellulose was coated 15%, and the soft capsule which manufactured solution prescription in the example 7-1 of oral tablet manufacture coated with the enteric nature coat was considered as the oral tablet.
[0044] The example 9-2 to 9-6 of manufacture: Although solution prescription was manufactured in the example 7-1 of oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 8-1 of manufacture using what was instead manufactured in the example 7-2 to 7-6 of manufacture, it considered as the oral tablet.
[0045] The example 10-1 of manufacture: According to the conventional method, azo polymer (example 12 of JP,3-7718,A) was coated 5% using the spray pan-coating machine, and the tablet which manufactured solution prescription in the example 8-1 of oral tablet manufacture coated with the enteric nature coat was considered as the oral tablet.
[0046] The example 10-2 to 10-6 of manufacture: Although solution prescription was manufactured in the example 8-1 of oral tablet manufacture coated with the enteric nature coat, by carrying out the same operation as the example 10-1 of manufacture using what was instead manufactured in the example 8-2 to 8-6 of manufacture, it considered as the oral tablet.
[0047] The example 1 of comparison: Using non PARERU (refined-sugar particle, 24 - 34 meshes) 500g as an oral tablet nucleus of powder prescription, with the centrifugal fluidized-bed-granulation machine which corns the following powder, by the conventional method, granulatio with a diameter of about 1mm was **(ed) and it considered as the oral tablet. Finally, the glycyrrhizin disodium salt became 39.4% among [all] the tablet, and a capric acid and sodium salt became about 17%.
[0048]
[Table 7]
** A part Loadings A glycyrrhizin disodium salt The 53 sections A capric acid and sodium salt The 25 sections Hydroxypropylcellulose (L-HPC) The 15 sections Microcrystalline cellulose (Avicel) The seven sections A total of 100 sections [0049] The example 2 of comparison: The tablet which manufactured powder prescription in the example 1 of oral tablet comparison coated with the enteric nature coat was coated with 10% and azo polymer (example 12 of JP,3-7718,A) 7% with carboxy methyl ethyl cellulose according to the conventional method using the spray pan-coating machine, and was considered as the oral tablet.
[0050] Internal use was carried out to the beagle which abstained from food overnight [example of experiment 1] by kg in 50mg /by having used ****** of the example 7-1 of manufacture, 8-1, 9-1, 10-1, the example 1 of comparison, and the example 2 of comparison as the glycyrrhizin disodium salt, and it administered intravenously by kg in 2mg /, and collected blood from the forearm vein with time, and plasma was obtained by the conventional method. The concentration of the glycyrrhizin in this plasma was measured by the high performance chromatography, and it asked for the curvilinear inferior-surface-of-tongue product (AUC and mg-min/ml) from 0 hour to [from the obtained concentration in plasma] 8 hours. The utilization factor was computed by comparison with intravenous administration. The result is shown in Table 1. Moreover, internal use of the glycyrrhizin oral tablet (100mg/(kg)) marketed the example 10-1 (50mg/(kg)) of manufacture and now is carried out to a beagle (3-6 animals), and the result which investigated concentration (average ** deflection) transition of the glycyrrhizin in plasma with time is shown in drawing 1 .
[0051]
[Table 8]
Table 1 Medication part Dose AUC (mg-min/ml) Utilization factor Solution A vein 2mg/kg 3408. 0 100% A commercial lock Taking orally 100mg/kg 310.2 0.2% The example 1 of comparison Taking orally 50mg/kg 653.4 0.8% Example of comparison 2 taking orally 50mg/kg 1202. 0 1.4% The example 7-1 of manufacture Taking orally 50mg/kg 2010. 0 2.4% Example 8-1 of manufacture Taking orally 50mg/kg 3378.0 4.0% Example 9-1 of manufacture Taking orally 50mg/kg 4656.2 Example 10-1 of 5.5% manufacture Taking orally 50mg/kg 5140.5 6.0% [0052] Consideration: The tablet of this invention showed the absorptivity which was extremely superior to the above-mentioned result compared with the oral tablet (example 2 of comparison) which coated a commercial oral tablet, the oral tablet (example 1 of comparison) of powder prescription, and powder prescription with the enteric nature coat. This enabled it to improve the absorptivity to the inside of the body in the internal use of glycyrrhizin and its salt.

[Translation done.]

* NOTICES *

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] With-time change of the glycyrrhizin concentration in plasma of the oral tablet of the example 10-1 of manufacture and marketing which carried out internal use is shown in a beagle.

[Translation done.]

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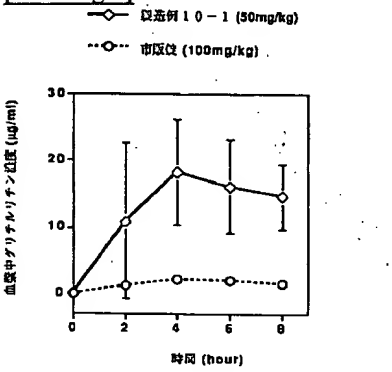
DRAWINGS

[Drawing 1]



[Translation done.]